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PNEUMONIA DUE TO TYPE V PNEUMOCOCCUS

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The separation of twenty-nine new types of pneumococci from those formerly designated as group IV opened up an entirely new and promising field for investigation. It was apparent that these new types required study along the same lines that had been applied to the original three types in order to determine variations in the clinical picture, the prognosis and especially the possibility of treatment with serum. Variations in diseases due to the pneumococci of types I, II and III are well known. In the case of infection with type I pneumococci the tendency to affect young adults, the more frequent acute and typical onset, the termination by crisis and the striking response to therapy with specific serum are recognized. Infection with type II pneumococci is associated with a more protracted and more irregular course, with a high incidence of invasion of the blood stream, numerous complications, less likelihood of critical termination, a higher mortality and less impressive response to serum therapy. In the case of infection with type III pneumococci a tendency to affect aged persons, especially those who are debilitated and infirm, a relatively low incidence of bacteremia but a high mortality rate and in the presence of bacteremia a uniformly fatal outcome and finally the complete absence of any response to serum therapy are recognized.

Since the group IV pneumococci are the incitants in only about 25 per cent of the cases of pneumonia it appeared probable that each of the constituent types would occur but rarely. It was found, however, that while most of the types did occur but rarely, types V, VII, VIII and XIV occurred with much greater frequency than the others. These types became, therefore, the object of our immediate interest. In this paper we report our experience with pneumonia due to type V pneumococci. Our experience with pneumonia due to the pneumococci of types VII, VIII and XIV will be reported in subsequent studies.

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INCIDENCE

Published reports of the incidence of type V pneumonia are scarce. Griffith found this type second in prevalence among the types into which he separated group IV; Robinson found this type, termed by him type IV E, the most common type during the winter of 1928 in Pittsburgh. No other reports are available.

During the past eight years (1928 to 1936) we observed one thousand, eight hundred and fifty cases of pneumococcic pneumonia. Sixty-eight of these were due to the type V pneumococcus, giving an incidence of 3.5 per cent.

Two features in the incidence of this disease have been impressive: (1) a tendency to epidemicity, evidenced by the fact that groups of four or five patients have on several occasions been admitted to the hospital within a few days, and (2) an apparent increase in frequency. Of the sixty-eight patients with type V pneumonia, twenty were seen in the four year period from 1928 to 1932, while forty-eight were seen in the following four year period, 1932 to 1936.

TABLE 1.—*Distribution of Sixty-Eight Cases of Type V Pneumonia by Year and Month*

	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	April	May	June	Total
1928-1929	..	..	..	..	..	..	1	..	1	..	2	..	4
1929-1930	..	..	..	..	2	1	..	..	..	..	..	..	3
1930-1931	..	..	..	..	..	..	5	1	1	..	1	..	8
1931-1932	..	..	..	..	..	2	..	1	1	1	..	..	5
1932-1933	..	1	1	..	..	..	2	4	1	1	..	..	10
1933-1934	..	..	..	1	1	1	1	2	1	1	1	..	9
1934-1935	..	..	..	..	..	..	..	3	5	2	2	1	13
1935-1936	..	..	1	..	..	..	6	4	1	4	..	..	16
Total	..	1	2	1	3	4	15	15	11	9	6	1	68

BACTERIOLOGY

The type V pneumococcus was originally designated by Avery as subgroup II A. He pointed out that strains of this type were agglutinated to a considerable degree by serum of type II pneumonia, although the agglutination was often delayed and incomplete. He noted, too, that type II antiserum protected to some extent against subgroup II A cultures, while antiserum for subgroup II A failed to protect against type II cultures.

In 1929 Cooper, Edwards and Rosenstein published their first paper reporting the separation of types among the pneumococci formerly called group IV. In that paper the strain described by Avery was designated as type V. It was shown that this organism when cultivated in blood broth mediums had a tendency to hemolyze red blood cells. In some strains this tendency was more marked than in others, but in general it was much greater than for the other pneumococci studied.

This organism, in contrast to many of the new types of pneumococci, must occur rarely if ever as a saprophyte in the mouths of normal persons. In no case in our experience was it found except in association with definite pneumonia.

ETIOLOGY

Certain factors which appeared to be predisposing were in general similar to those found in other types of pneumonia. Outstanding among these was infection of the upper respiratory tract, usually a common cold. This infection was present in thirty-four of the sixty-eight cases. There was a history of exposure in twenty, of trauma in two, of alcoholic stupor in three and of dietary deficiency in three. In three cases pneumonia was associated with pregnancy. In one case in which pneumonia developed while the patient was in the ward, definite contact infection was evident.

SEX AND AGE

Only seven of the sixty-eight patients were females, that is, 10.2 per cent of the group. No significance is attached to this, because pneumococcic pneumonia is predominantly a disease of males.

The ages of the patients were scattered fairly evenly, except in the fourth decade, in which age group belonged twenty-four of the sixty-eight patients.

CLINICAL PICTURE

Onset.—In forty-six cases the onset of the disease was abrupt and was associated with sharp shaking chill, thoracic pain and cough and in thirty-eight cases with the expectoration of rusty or frankly hemorrhagic sputum.

In twenty-two cases the onset was atypical, occurring usually in the course of some infection of the upper respiratory tract, and characterized as a rule by irregular fever without chill.

Fever.—The fever was usually of the plateau type, and in a high percentage of cases termination was by crisis. In thirteen of the eighteen cases in which recovery was obtained without serum treatment there was termination by crisis. In fifteen of the twenty-nine cases in which serum treatment was given the disease terminated by crisis.

The duration of fever tended to be prolonged. In only seven of the twenty-nine cases in which recovery occurred without serum was there termination of fever in less than one week, while in eleven cases it lasted one week or more, in three of these cases lasting more than ten days.

Headache.—In twenty cases headache was a symptom early in the disease. Usually it was severe; in one case it was so severe that the presence of meningitis was suspected.

Vomiting.—Vomiting occurred in nineteen cases. In several of these it was persistent, and in three it was associated with severe diarrhea.

Jaundice.—The frequency with which jaundice occurred was striking. It was present in sixteen cases, a frequency several times that usually encountered. It seems not unlikely that this frequency is related to the hemolytic properties of the type V pneumococcus.

Bacteremia.—Culture of the blood was made in every case as soon as possible and before the administration of serum. If the culture showed a positive result it was repeated every day until the result was negative. If the first culture showed a negative result, another was made only if there was a chill, a sudden sharp rise in temperature, persistent fever or some complication.

In eighteen of the sixty-eight cases culture showed positive results when the patient was admitted to the hospital. In addition, in two cases in which the result was at first negative, later there was a positive result. Bacteremia was therefore present in twenty cases, an incidence of 29 per cent. This is a higher incidence of bacteremia than for any other type of pneumonia in our experience.

Anoxemia.—The presence of anoxemia was indicated by cyanosis and tachypnea and in four cases by the estimation of the oxygen saturation in the arterial blood. In five cases anoxemia was so marked that this feature dominated the clinical picture. In eleven cases there was anoxemia of moderate grade. In practically all the other cases a slight degree of cyanosis was noted at some period of the disease.

Severity.—In general the severity of any type of pneumonia is directly related to the following factors: (1) bacteremia, (2) anoxemia, (3) the age of the patient and (4) his general state of health.

Using these factors we made in each case an estimation of the severity of the disease. In twelve cases we found it to be extremely severe, with overwhelming infection. In some of these cases there was profuse bacteremia; in one case there were 2,000 colonies per hundred cubic centimeters of blood and in another 1,200 colonies. There were also cases of meningitis and of acute bacterial endocarditis. In thirty-eight cases the disease was estimated to be moderately severe, and in only eighteen cases could the disease be regarded as mild.

SERUM TREATMENT

The successful use of serum therapy in pneumonia depends on the potency of the specific antiserum and its administration early in the course of the disease. From experience with serum for type I and type II pneumonia it is generally believed that the first two days com-

prise the most favorable period for administration and that with each day thereafter the result becomes less favorable.

In thirty-nine of our cases serum treatment was given, and in only twelve cases was it given within the first three days. In the other cases treatment was given at a later period, in nine of these cases being given later than one week after the onset.

A comparison between the results in the cases in which serum was given and in those in which it was not given is shown in table 2.

The importance of early serum therapy is suggested by the comparison of results in cases in which treatment was given early and of those in which it was given late. In only two of the twelve cases in which treatment was given within the first three days did death occur. In only three of the twenty-five cases in which treatment was given within the first five days did death occur. When treatment was begun after the fifth day the mortality rate rose rapidly, death occurring in seven of the thirteen cases.

TABLE 2.—*Mortality with Regard to Serum Treatment*

	Nonserum Treatment			Serum Treatment		
Cultures of Blood	Number of Cases	Number of Deaths	Mortality, Percentage	Number of Cases	Number of Deaths	Mortality, Percentage
Negative results	19	4	21	31	5	16
Positive results	10	7	70	8	5	62
Whole series	29	11	38	39	10	26

In presenting the results of serum treatment in so small a series of cases we are conscious of the limited value of the figures. However, it is our expectation that similar reports will soon be forthcoming from other institutions and that all these reports when pooled may constitute a group sufficiently large to be significant.

COMPLICATIONS

The most common complication was empyema, which occurred in seven cases. In only two of these cases had serum treatment been given.

Endocarditis was proved at autopsy in two cases. In a third case there was all the evidence usually regarded as sufficient for the diagnosis, but autopsy was not performed.

Suppurative bronchitis was present in three cases. Meningitis was present in two cases, and each of the following conditions was noted once: Otitis media, pleurisy with effusion, pulmonary abscess, purulent pericarditis, embolism of the subclavian artery and glomerular nephritis.

TABLE 3.—*Analysis of Ten Fatal Cases in Which Serum Treatment was Given*

Case No.	Age	Sex	Alcohol	Results of Blood Culture	Anoxemia	Start of Serum Treatment, Day	Total Serum, Units	Clinical Notes	Autopsy Observations
4	42	M	++++	Negative	Cyanosis +++	6	64,000	Hemoglobin, 45%; erythrocytes,2,800,000; jaundice	Consolidation of three lobes
8	33	M	0	Negative	Cyanosis +++	Indef.	87,000	Hemoglobin, 69%; severe jaundice	
9	70	M	0	Positive	Cyanosis ++	3	258,000	Arteriosclerotic heart disease; bundle branch block; coronary sclerosis	Acute and chronic endocarditis; coronary sclerosis; enlargement of heart; acute fibrinous pleurisy with effusion
11	44	M	++++	Positive	82.8% saturation of oxygen	7	27,200	Hemoglobin, 35%; erythrocytes,3,500,000; jaundice	
13	32	M	0	Negative	Cyanosis +++	2	24,000	Malignant nephrosclerosis complicated by pneumonia; blood pressure, 260/170; nonprotein nitrogen, 180 mg.; death in uremia	Advanced nephrosclerosis of arterial and arteriolar varieties
26	39	M	0	1,200 colonies	Cyanosis ++	7	562,500	Jaundice	Encapsulated empyema; acute diffuse fibrinopurulent pericarditis; acute fibrinopurulent endobronchitis
34	28	F	0	Positive Negative Positive	Cyanosis ++++	5	750,000	Pregnancy of 5 mo.; abortion; meningitis; empyema; embolism of subclavian artery; jaundice	Acute bacterial endocarditis; empyema; embolism of left subclavian artery
45	37	M	0	100 colonies 40 colonies 210 colonies	Cyanosis ++	6	500,000	Chronic lymphatic leukemia; jaundice	
52	62	M	0	Negative	Cyanosis ++	7	105,000	Jaundice	Pulmonary abscess; purulent bronchitis involving four lobes
55	55	M	0	Negative	Cyanosis +++	9	109,000	Delay in determining type; no sputum	

SUMMARY

Sixty-eight cases of pneumonia due to type V pneumococcus were studied. The distribution of these cases by months and years suggests an increasing frequency and a tendency to epidemicity.

The clinical course was characterized in most cases by an abrupt onset and a prolonged course, and in over half the cases there was termination with crisis. Headache, vomiting and jaundice were common symptoms. There was a high incidence of bacteremia and anoxemia. Complications were frequent.

In the cases in which serum treatment was given there was a lower mortality than in the cases in which serum treatment was not given. The difference was especially marked in those cases in which treatment was given early in the course of the disease.

The common concept that group IV pneumonia is always a mild infection is contradicted by this study.

EFFECT OF OXYGEN INJECTED SUBCUTANEOUSLY ON ANTIBODY FORMATION

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In a communication by Barker and one of us (T. S.)[1] the effect of the subcutaneous administration of oxygen on experimentally induced anoxemia in dogs was discussed. The failure of the injected oxygen to alter the oxygen content or percentage of desaturation of the arterial blood and the lack of evidence of absorption of the injected oxygen indicate little therapeutic value for its use. However, favorable clinical results have frequently been reported, and the possibility that oxygen given subcutaneously may exert some indirect effect by stimulating the antibody-producing mechanism cannot be ignored, especially in view of the following report from the literature.

Lipkin, Podvalny and Grintzevic[2] have reported on the effect of the subcutaneous administration of oxygen on the titer of complement and natural hemolysin for sheep red blood cells in normal dogs and on agglutinin formation in the dogs after injections of typhoid vaccine. The titers of complement and natural hemolysin were determined for three dogs both before and after the subcutaneous injection of oxygen, the dogs receiving 30, 20 and 10 cc., respectively, of oxygen per kilogram. The complement titers decreased threefold within twenty-five days. The natural hemolysin titers decreased tenfold within eight days after the injection of oxygen and disappeared entirely within twenty-five days. To determine the effect of the subcutaneous administration of oxygen on the specific antibody response, five dogs were given typhoid

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1. Simpson, T., and Barker, M. H.: A Study in Subcutaneous Oxygen Therapy, Arch. Int. Med., to be published.

2. Lipkin, J. J.; Podvalny, P. B., and Grintzevic, O.: The Action of Subcutaneous Oxygen on the Variation of Complement, Hemolysin, and on the Formation of Specific Antibodies, Gior. di batteriol. e immunol. **13**:661, 1934.

vaccine in increasing amounts every day for ten days. Eight days after the last injection of antigen one dog was given 30 cc. of oxygen per kilogram of body weight subcutaneously, the injections being continued daily for eight days. Two other dogs were given 30 and 20 cc., respectively, of oxygen per kilogram along with the injections of antigen, the two remaining dogs serving as controls. A fourfold increase in specific agglutinin titer was obtained in the dog receiving 20 cc. of oxygen per kilogram within twenty days after the last injection of antigen and an eightfold increase within sixteen and twenty days, respectively, in the two dogs receiving 30 cc. of oxygen per kilogram of body weight. The authors concluded that the subcutaneous introduction of oxygen caused a decrease in natural complement and hemolysin, while it stimulated the formation of specific antibodies. The importance of these results, if substantiated, is obvious. However, the number of animals used and the number of determinations made were few.

In order to determine the effect of the subcutaneous injection of oxygen on specific antibody response to the parenteral injection of bacterial antigen and on the complement titer, the following experiments were carried out:

METHODS

Six dogs weighing from 10 to 16 kilograms and ten rabbits weighing from 2 to 3 kilograms were given intravenous injections of a heat-killed suspension of type I and type II pneumococci containing approximately 2,000,000,000 organisms of each type per cubic centimeter. The dogs were given injections of increasing amounts of the antigen for ten successive days, each receiving a total of approximately 12.5 billion pneumococci of each type; the rabbits were given five successive daily injections, each receiving a total of approximately 6,500,000,000 pneumococci.

Five of the ten rabbits were given daily subcutaneous injections of approximately 30 cc. of oxygen per kilogram of body weight, beginning on the day of the first injection of antigen and continuing throughout the course of the experiment. Three of the six dogs received similar daily subcutaneous injections of oxygen, starting the seventh day after the last injection of antigen and continuing throughout the course of the experiment. At no time was there evidence of complete absorption of the injected oxygen. A large excess was always present.

All animals were tested, both before immunization and at three day intervals after the last injection of antigen, for agglutinins and opsonins for type I and type II pneumococci. In addition, complement titrations were made for all rabbit serums.

The agglutination tests were set up, the usual serial dilution method being used to the limit of titer. Living type I and type II pneumococci, centrifugated from twenty-four hour dextrose broth cultures and resuspended in physiologic solution of sodium chloride, were used as antigens in the test. The tubes were incubated two hours at 37 C., and a reading was made after they had stood overnight in the icebox.

The opsonin content of the serums was determined by using the Jung [3] modification of the Wright capillary pipet method. Normal whole blood of dogs was washed carefully four times with physiologic solution of sodium chloride, the leukocytes were counted and the blood was diluted with physiologic solution of sodium chloride to obtain a concentration of 10,000 leukocytes per cubic millimeter. Standard heat-killed suspensions of type I and type II pneumococci were employed throughout. Two volumes of standardized blood, 1 volume of bacterial suspension and 1 volume of undiluted serum were carefully mixed in a capillary pipet and incubated for thirty minutes at 37 C. For the controls, physiologic solution of sodium chloride was substituted for serum. Smears were made on clean glass slides and stained with the Wright stain. One hundred cells were counted on each slide, and the results were recorded as the percentage of cells showing phagocytosis.

Rabbit complement titers were determined as follows: To a series of tubes undiluted rabbit serum was added in amounts varying from 0.02 to 0.2 cc., increasing by steps of 0.02 cc. Sufficient physiologic solution of sodium chloride was then added to make the volume 1 cc. One-tenth cubic centimeter of hemolytic amboceptor, containing 2 units, and 1 cc. of a 1 per cent suspension of sheep red blood cells were added to give a total volume of 2.1 cc. The results were read after incubation for one hour at 37 C. The titer was recorded as the least amount of serum giving complete hemolysis.

RESULTS

Agglutinins.—The agglutinin response was markedly greater in rabbits into which type I and type II pneumococci had been injected than in dogs into which the same organisms had been injected. Likewise, the agglutinin titers for type I pneumococci were much greater than for type II pneumococci, in the case of rabbits the total average titer being twenty-five times as great and in the dogs six times as great (tables 1 and 2).

There was no significant difference between the total average agglutinin titers of the oxygen-treated and the control animals for type II pneumococci. In fact, although there were minor differences in the separate sets of determinations between the oxygen-treated and the control group, the total average agglutinin titers of the rabbits were almost the same in the two groups, and the control group of dogs had a slightly higher average agglutinin titer. The same applied to the total average agglutinin titers for type I pneumococci of the dogs (tables 1 and 2).

The average agglutinin titers for type I pneumococci of the rabbits showed greater differences between the oxygen-treated and the control animals (table 1). The maximum titers were reached on the sixth day in the oxygen-treated rabbits, with an average of 1:1,408, and on the twelfth day in the controls, with an average titer of 1:864. By the twenty-first day the two groups gave approximately the same average

3. Jung, R. W.: The importance of Leucocyte Counts in Phagocytic Tests, J. Lab. & Clin. Med. **21**:760, 1936.

TABLE 1.— *Agglutinin Titers of Rabbits and Dogs for Type I Pneumococci*

Animal No.	B*	Time After Last Injection of Antigen, Days: 3	6	9	12	15	18	21	Total Average Titer
Rabbits, oxygen-treated									
1	10	320	1,280	1,280	1,280	640	640	320	
2	0	160	1,280	640	640	640	640	320	
3	0	40	640	640	640	320	320	320	
4	0	1,280	2,560	2,560	1,280	640	640	640	
5	0	640	1,280	1,280	1,280	640	320	320	
Average		488	1,408	1,280	1,024	576	512	384	810
Rabbits, controls									
6	0	160	1,280	1,280	1,280	640	320	320	
7	0	20	160	160	320	320	320	dead	
8	0	160	1,280	1,280	1,280	640	640	640	
9	0	320	1,280	1,280	1,280	640	320	320	
10	0	20	160	160	160	160	160	160	
Average		136	832	832	864	480	352	360	550
Dogs, oxygen-treated									
1	0	20	80	160	160	20	80	80	
2	0	0	80	160	160	40	80	80	
3	0	20	80	320	320	80	160	80	
Average		13.3	80	213	213	46.6	106	80	107
Dogs, controls									
4	20	80	160	160	320	80	80	80	
5	0	20	40	80	320	40	160	160	
6	0	40	160	160	80	20	80	80	
Average		46.6	120	133	240	46.6	106	106	114

* In tables 1, 2, 5 and 6 B indicates before the injection of antigen.

TABLE 2.—*Agglutinin Titers of Rabbits and Dogs for Type II Pneumococci*

Animal No.	B	Time After Last Injection of Antigen, Days: 3	6	9	12	15	18	21	Total Average Titer
Rabbits, oxygen-treated									
1	0	0	40	20	40	10	10	10	
2	0	0	80	20	20	10	0	0	
3	0	0	20	20	20	10	10	10	
4	0	160	40	40	40	40	40	20	
5	0	80	20	40	40	20	20	20	
Average		48	40	28	32	18	16	12	27.7
Rabbits, controls									
6	0	0	20	20	20	10	20	20	
7	0	0	0	20	20	40	20	dead	
8	0	0	0	40	40	20	20	20	
9	0	80	20	20	20	0	0	0	
10	0	0	40	80	160	80	40	20	
Average		16	16	36	52	30	20	15	26.4
Dogs, oxygen-treated									
1	0	0	80	10	20	0	0	0	
2	0	0	80	20	20	10	0	0	
3	0	0	40	20	20	0	0	0	
Average		0	66	16	20	3	0	0	15
Dogs, controls									
4	0	0	160	40	20	20	0	0	
5	0	0	80	0	20	10	0	0	
6	0	0	40	40	40	0	0	0	
Average		0	93	26	26	10	0	0	22

titer. The total average agglutinin titer of the oxygen-treated rabbits was 1 : 810, and that of the untreated controls was 1 : 550, a difference of 260. The greatest difference between the average agglutinin titers of the two groups was obtained on the sixth day, the titers for the treated rabbits averaging 576 higher than those for the controls. In view, however, of the extreme variation in the agglutinin response of the individual rabbits, the significance of these differences is open to question. A statistical study, with computation of the probable error and of the probability that the results were due to chance, showed that in none of the individual sets of determinations was the probability that the results were due to chance less than 1 : 7, which is too high to permit of these differences being called significant (table 3). The probability that the difference in the total average agglutinin titers was due to chance was 1 : 22, which falls in the same category.

TABLE 3.—*Significance of Differences in Average Agglutinin Titers for Type I Pneumococci*

	Time After Last Injection of Antigen, Days							Total Average Titer
	3	6	9	12	15	18	21	
Average titer for oxygen-treated rabbits	488	1,408	1,280	1,024	576	512	384	810
Average titer for control rabbits	136	832	832	864	480	352	360	550
Difference	352	576	448	160	96	160	24	260
Probability that difference was due to chance	1:7	1:6	1:3	1:2	1:2	1:6	1:1	1:22

Opsonins.—Normal dog and rabbit serums opsonized both type I and type II pneumococci. Type I pneumococci were phagocytosed to the same extent in both normal dog and normal rabbit serum, averaging 43.9 per cent. Normal rabbit serums averaged only 7.7 per cent, and normal dog serums averaged 27.6 per cent phagocytosis of type II pneumococci (tables 4 and 5).

The average increase in phagocytosis of pneumococci following injection of antigen of type I and type II pneumococci was approximately 10 per cent higher in dog than in rabbit serums. The total average increase was about the same for both type I and type II pneumococci in dog and rabbit serums. This is not at all comparable to the agglutinin response. The rabbits produced higher agglutinin titers for both organisms than did the dogs, and the agglutinin titers for type I pneumococci were considerably higher than those for type II pneumococci in both dogs and rabbits.

When the total average increase in percentage of phagocytosis for both type I and type II pneumococci in serums of the oxygen-treated animals is compared with that for the controls, it can readily be seen that there is no significant difference (tables 4 and 5).

TABLE 4.—*Percentage of Phagocytosis of Type I Pneumococci in Rabbit and Dog Serums*

Animal No.	B	Time After Last Injection of Antigen, Days							Total Average Phagocytosis	
		3	6	9	12	15	18	21	%	Increase, %
Rabbits, oxygen-treated										
1	43	71	52	36	75	76	82	63		
2	46	71	54	74	60	58	78	78		
3	49	61	54	73	63	68	87	70		
4	46	72	83	83	66	53	64	72		
5	38	66	71	80	71	63	89	86		
Average	44.4	68.2	62.8	69.2	67	63.6	80	73.8	69.2	24.8
Rabbits, controls										
6	40	67	76	84	73	80	89	76		
7	42	55	68	52	66	84	83	dead		
8	47	68	80	71	73	73	91	66		
9	40	63	83	69	89	83	95	75		
10	42	52	57	64	69	62	72	64		
Average	42.2	61	72.8	68	74	76.4	86	70.2	72.5	30.3
Dogs, oxygen-treated										
1	42	81	73	54	82	83	95	89		
3	47	81	85	82	88	89	94	87		
3	46	68	84	86	91	94	91	90		
Average	45	76.4	80.6	74	87	88.6	93.3	85.3	83.6	38.6
Dogs, controls										
4	44	80	72	67	78	90	92	90		
5	44	80	88	78	89	86	94	87		
6	45	78	91	75	78	91	92	87		
Average	44.3	79.3	83.6	73.3	81.6	89	92.6	88	83.9	39.6

TABLE 5.—*Percentage of Phagocytosis of Type II Pneumococci in Rabbit and Dog Serums*

Animal No.	B	Time After Last Injection of Antigen, Days							Total Average Phagocytosis	
		3	6	9	12	15	18	21	%	Increase, %
Rabbits, oxygen-treated										
1	9	19	57	37	31	11	23	8		
2	6	7	27	22	23	2	18	7		
3	8	14	65	58	24	16	24	12		
4	6	80	87	80	57	38	53	22		
5	9	50	76	73	62	16	28	15		
Average	7.6	34	62.4	54	39.4	16.6	29.2	12.8	35.5	27.9
Rabbits, controls										
6	11	29	77	42	33	18	13	6		
7	7	11	11	23	30	25	16	dead		
8	10	11	72	33	43	14	29	5		
9	5	21	45	37	47	8	26	18		
10	6	2	35	65	70	33	61	55		
Average	7.8	14.8	48	40	44.6	19.6	29	21	31.0	23.2
Dogs, oxygen-treated										
1	24	63	67	51	71	73	76	60		
2	28	61	64	71	71	46	72	60		
3	23	41	77	77	66	35	70	50		
Average	25	55	69.3	66.3	69.3	51.3	72.6	56.6	62.9	37.9
Dogs, controls										
4	32	63	59	57	79	85	79	80		
5	30	74	63	76	75	75	46	70		
6	29	71	73	51	57	48	34	49		
Average	30.3	69.3	65	61.3	70.3	69.3	53	66.3	64.9	34.6

Complement.—Complement titrations were made only for rabbit serums. There was considerable variation in the normal complement concentrations among the individual rabbits. After the injections of antigen the average amount of complement rose slightly and maintained a fairly constant level, with a few minor variations, throughout the following three weeks. The oxygen-treated rabbits showed an average of only 0.005 cc. more complement than the controls, a difference that is without significance. These results are in marked contrast to those of Lipkin, Podvalny and Grintzevic,[2] who observed a marked decrease in complement titer for dogs given oxygen subcutaneously.

TABLE 6.—*Complement Titers for Rabbits*

		Time After Last Injection of Antigen, Days							Total Average	Total Average
Rabbit No.	B	3	6	9	12	15	18	21	Titer	Increase
Oxygen-treated										
1	0.14	0.06	0.04	0.01	0.06	0.06	0.06	0.06		
2	0.02	0.08	0.08	0.18	0.10	0.10	0.12	0.10		
3	0.12	0.06	0.00	0.16	0.08	0.10	0.08	0.10		
4	0.06	0.06	0.06	0.18	0.10	0.06	0.06	0.06		
5	0.14	0.06	0.08	0.18	0.10	0.08	0.08	0.10		
Average	0.116	0.064	0.052	0.16	0.088	0.08	0.08	0.084	0.084	0.029
Controls										
6	0.14	0.04	0.04	0.14	0.04	0.06	0.08	0.08		
7	0.14	0.02	0.04	0.18	0.14	0.16	0.18	dead		
8	0.12	0.06	0.04	0.10	0.04	0.06	0.06	0.08		
9	0.10	0.06	0.06	0.10	0.08	0.06	0.10	0.08		
10	0.06	0.08	0.08	0.10	0.04	0.08	0.10	0.10		
Average	0.112	0.072	0.072	0.124	0.088	0.084	0.104	0.085	0.089	0.023

COMMENT

The lack of any observable effect of the subcutaneous injection of oxygen on the production of agglutinin and opsonin in rabbits and dogs and on the complement titers of rabbits might be considered surprising, in view of the marked effect reported by Lipkin, Podvalny and Grintzevic.[2] However, a critical examination of their data reveals that, owing to the small number of animals employed and the few determinations made, the possibility that their results were due to random sampling was great. This possibility is brought out clearly in our work if the extreme variation in formation of antibodies by the individual animals is observed. This is especially pronounced in the agglutinin titers of rabbits for type I pneumococci (table 1). By comparing only the rabbit in the oxygen-treated group producing the highest titer with the control rabbit producing the lowest titer, the effect of treatment with oxygen would have been to increase the agglutinin content eightfold. Conversely, it would be possible by appropriate selection to obtain a control rabbit with a titer four times as high as that of an oxygen-treated rabbit. The results

show that with relatively large groups of treated and control animals these discrepancies in individual response are minimized. Furthermore, statistical examination is a valuable aid in determining the true significance of observed differences.

From a physiologic point of view this lack of effect is not surprising, especially in view of the recent work [1] showing the lack of utilization by the anoxemic dog of oxygen injected subcutaneously. Even if an excess of oxygen could affect the antibody-producing mechanism, this lack of utilization would preclude its reaching the site of antibody formation and hence its exciting any effect. Furthermore, it is difficult to understand why as slight an amount of oxygen as would be obtained by the subcutaneous route, even if it were all absorbed, would stimulate antibody formation when oxygen is normally absorbed in far greater quantities by way of the respiratory tract.

SUMMARY

A study was made of the effect of the subcutaneous administration of oxygen on the production of agglutinin and opsonin in rabbits and dogs into which heat-killed type I and type II pneumococci had been injected and on the complement titers of rabbits.

Into ten rabbits and six dogs were injected heat-killed pneumococci of type I and type II. Half were given daily subcutaneous injections of 30 cc. of oxygen per kilogram of body weight, the remainder being used as controls. Determinations of the opsonin and agglutinin contents of the serums were made for all the animals at frequent intervals over a period of three weeks after the last injection of antigen. Complement titrations were made at the same time for all rabbit serums.

The subcutaneous administration of oxygen had no effect on the opsonin content of the serums of the dogs or rabbits for either type I or type II pneumococci.

The subcutaneous administration of oxygen had no effect on the agglutinin titers of dog serums for type I and type II pneumococci nor had it any effect on the agglutinin titers of rabbit serums for type II pneumococci.

An apparent effect of the subcutaneous injection of oxygen on the agglutinin titers of rabbits for type I pneumococci was found statistically to be without significance.

CLASSIFICATION AND TERMINOLOGY OF LEUKEMIA AND ALLIED DISORDERS

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Hughes Bennett [1] proposed the term leukocythemia and Virchow [2] the term *Leukämie* almost simultaneously in 1845 to designate the disease which is now regarded almost uniformly by English speaking physicians as leukemia. Later two types were differentiated and called splenomyelogenous leukemia and lymphatic leukemia. Reschad and Schilling-Torgau,[3] in 1913, described a third common type, monocytic leukemia. A number of other types of leukemia or related disorders are reported on frequently in the medical literature, among these being chloroleukemia, leukosarcoma, plasma cell leukemia, eosinophilic leukemia, basophilic leukemia, megakaryocytic leukemia, leukanemia, pseudoleukemia, aleukemic leukemia and others to be mentioned later.

There has been a tendency in recent years to substitute the terms leukosis, myelosis and lymphadenosis for leukemia, myelogenous leukemia and lymphogenous leukemia, respectively. The reasons presented for the substitution of these newer terms for the older equivalents are that the newer terms are said to indicate more fundamental hematopoietic changes. It is well to bear in mind, however, that the term leukemia is well defined in much the same manner as is the term anemia. Obviously both are incorrect if one wishes to translate them literally. Perhaps in the future, with advancement of knowledge, a more precise designation may be possible, but in the present state of inadequate knowledge it appears both unwise and unnecessary to adopt new terms or additional equivalent terms to describe pathologic states already well described by a terminology which has existed for many decades.

Because of these and other complicating factors students and physicians frequently are confused concerning the classification and termi-

From the Department of Medicine of the Peiping Union Medical College.

1. Bennett, J. H.: Case of Hypertrophy of the Spleen and Liver, in Which Death Took Place from Suppuration of the Blood, Edinburgh M. & S. J. **64**:413, 1845.

2. Virchow, R.: Weisses Blut, Notiz. a. d. Geb. d. Nat.- u. Heilk. **33**:151, 1845.

3. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wchnschr. **60**:1981, 1913.

nology of leukemia. That the disease or diseases in all variations may be designated by a simple terminology and classified in a rational and uniform manner is shown in the following paragraphs.

Leukemia, in general, is classified on the basis of whether it is acute or chronic, leukemic or subleukemic (aleukemic). It is common practice to combine with these clinical terms the anatomic name of the strain of cells which plays the dominant rôle in the leukemic process. Thus one may speak of acute lymphocytic leukemia, chronic monocytic leukemia and other types. Some workers prefer to indicate the origin of the cells which are concerned and to designate the types as myelogenous (myeloid or medullary) leukemia or lymphogenous (lymphoid or lymphatic) leukemia. Still other workers choose to make use of the conventional nomenclature for neoplastic diseases and designate the types of leukemia by such terms as leukemic lymphoblastoma, leukemic myeloblastoma or leukemic monoblastoma (table 1).

All variations and combinations of the aforementioned terms are in common use, but rarely does one find that an author is consistent in adhering to any one of the systems mentioned. Thus, many workers speak of myelogenous and lymphatic leukemia, whereas it would be more proper to speak of myelogenous and lymphogenous leukemia. I can find no justification for the use of the term lymphatic to designate the type of leukemia in which lymphocytic cells are the chief elements concerned. Furthermore, there is no comparable term to designate leukemia arising from the cells of the bone marrow. Neither does there seem to be any reason for using the terms myeloid and lymphoid when myelogenous and lymphogenous are meant.

Myelogenous leukemia obviously is a general term indicating that the cells of the leukemic process arise from the bone marrow. Therefore it should be applicable to the types of leukemia in which basophilic, eosinophilic, neutrophilic and megakaryocytic leukocytes, respectively, or their precursors are concerned. This, however, is not the usual practice. The term myelogenous leukemia is used commonly to designate that type of leukemia in which neutrophilic leukocytes and their precursors are the cells involved. This usage has been carried over from the early workers, who were not aware that myelogenous leukemia of other types occurred. Some physicians have substituted the term myelocytic leukemia. This also is undesirable, since myelocytes of different types occur and the designation is not specific.

In order to clarify and simplify the classification of leukemia, it is suggested that some such plan as that outlined in the accompanying table (table 2) be followed. According to this plan the disease commonly referred to as chronic myelogenous leukemia would be more specifically designated as chronic neutrophilocytic leukemia. This

term would be comparable to chronic lymphocytic or chronic monocytic leukemia. If less specific designation is made necessary or is desirable, one may speak properly of chronic myelogenous or chronic lymphogenous leukemia.

TABLE 1.—*Classification of Leukemia and New Growths of the Hematopoietic System Based on the Conventional Nomenclature for Neoplasms* *

Normal Cells in Hematopoietic Organs	Conventional Nomenclature of Neoplasms Applied to Cells of Hematopoietic Organs	Types of Leukemia and of Some Other Diseases Classified Under the Name of the Tumor
Polymorphonuclear leukocytes and their precursors—myelocytes and myeloblasts	Myeloblastoma	1. Myelosarcoma 2. Chloroleukemia or chloroleukosarcoma or chloroma 3. Neutrophilocytic, basophilocytic or eosinophilocytic leukemia 4. Myeloblastic leukemia
Lymphocytes and lymphoblasts	Lymphoblastoma	1. Lymphosarcoma 2. Leukosarcoma 3. Lymphocytic leukemia 4. Lymphoblastic leukemia 5. ? Lymphogranuloma (Hodgkin's disease) 6. ? Small round cell sarcoma 7. ? Mycosis fungoides
Monocytes and monoblasts	Monoblastoma	1. Monosarcoma 2. Monocytic leukemia
Megakaryocytes and megakaryoblasts	Megakaryoblastoma	1. Megakaryocytic leukemia 2. Megakaryoblastic leukemia 3. ? Lymphogranuloma (Hodgkin's disease)
Plasma cells	Plasmoma or plasmacytoma	1. Plasma cell myeloma 2. Plasma cell leukemia 3. Plasmacytoma
Erythrocytes and their precursors—reticulocytes, normoblasts, erythroblasts and megaloblasts	Erythroblastoma	1. Erythrosarcoma 2. ? Erythroblastic anemia 3. ? Erythremia (polycythaemia vera)
Mesenchyme cells (primitive fibroblasts, primitive connective tissue cells, reticular cells of the reticular syncytium)	Reticuloma or reticular cytoma	1. Reticulum cell sarcoma 2. Stem cell (hemohistioblastic or embryonal cell or lymphoidocytic) leukemia
Macrophages (histiocytes, clasmatocytes, reticuloendothelial cells)	Histioblastoma or reticulo-endothelioma	1. Histioblastoma or reticuloendothelioma 2. Xanthoma (diseases of Gaucher, Niemann-Pick and Christian)
Endothelial cells of common blood and lymph vessels	Endothelioma	1. Hemangio-endothelioma 2. Lymphangio-endothelioma 3. ? Perithelioma
Fibrocytes and fibroblasts	Fibroblastoma	1. Fibrosarcoma

* Modified from Forkner, C. E.: Leukemia, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4.

TERMINOLOGY OF MONOCYTIC LEUKEMIA

The origin of the monocyte is still controversial. Some workers believe that monocytes arise from myeloblasts in the bone marrow; others, that they are derived from lymphoid cells, and still others, that they develop from primitive mesenchyme cells, from fibroblasts or from

TABLE 2.—*Classification of Leukemia (Leucemia, Leukosis, Leucocythemia)**

Clinical Designation	General Type of Leukemia	Cell of Origin	Specific Type of Leukemia†	Synonyms Depending on Common Usage, on Course of Disease or on Clinical or Hematologic Characteristics
Leukemia or subleukemic (aleukemic) leukemia (acute or chronic)	Myelogenous (arising from cells or bone marrow)	Myeloblast	NEUTROPHILOCYTIC LEUKEMIA	Myelogenous, myeloid, myelocytic or myeloblastic leukemia; myelosis
			Eosinophilocytic leukemia	Eosinophilic leukemia
			Basophilocytic leukemia	Basophilic leukemia
			Chloroleukemia	Chloroma or chloroleukosarcoma
		Myeloblast and megaloblast	Erythroleukemia	Leukemia associated with erythremia
		Megakaryoblast	Megakaryocytic leukemia	
	Lymphogenous (arising from cells of lymphoid tissue)	Lymphoblast	LYMPHOCYTIC LEUKEMIA	Lymphogenous, lymphoid, lymphatic or lymphoblastic leukemia; lymphoblastoma leukaemicum; lymphadenosis
			Leukosarcoma	Lymphosarcoma associated with leukemia
	Lymphogenous or myelogenous	Primitive mesenchyme cell	Stem cell leukemia	Hemohistioblastic, embryonal or lymphoidocytic leukemia
		Plasma cell, myeloblast and lymphoblast	Plasma cell leukemia	Plasmacytoma with leukemia or multiple myeloma with leukemia
	Disputed	Monoblast	MONOCYTIC LEUKEMIA	Histiocytic leukemia; reticulosis; reticulo-endotheliosis, reticulum cell leukemia; reticulosarcoma

* Modified from Forkner, C. E.: Leukemia, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1937, vol. 4.
† The common types are given in capital letters.

macrophages. Hence one cannot speak of monocytic leukemia in terms of the origin of the type cell.

Some workers, particularly Naegeli,[4] Piney,[5] Anagnostu,[6] Kracke and Garver [7] and others, owing to the fact that they have regarded the monocyte as a derivative of the myeloblast, have not accepted monocytic leukemia as a distinct disease entity but have regarded it as a transitory phase in myelogenous leukemia. Reich [8] and Fontana [9] have presented patients with conditions believed to be due to monocytic leukemia, but the conditions subsequently were said to be considered as having been transformed into myelogenous leukemia. The evidence for this apparent transformation was that at first the blood contained predominatingly cells resembling monocytes, but as the terminal stage approached the predominating cells resembled myeloblasts. Farrar and Cameron [10] have discussed this question. Obviously the blast cells of each of the various kinds of leukocytes are difficult to differentiate. It is only by the use of all available methods that definite conclusions may be reached. The evidence seems insufficient to justify the acceptance of a transformation of one type of leukemia into another.

Space does not permit a detailed discussion of the origin and independence of the monocyte. This has been the subject of much controversy during the past twenty years. I [11] reviewed the problem on two occasions, and more recently Doan and Wiseman [12] published

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4. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923.

5. Piney, A.: Recent Advances in Hematology, London, J. & A. Churchill, 1928.

6. Anagnostu, J.: Ueber einen seltenen Fall von chronischer monozytoider Promyelozyten-Leukämie, Folia haemat. **43**:446, 1931.

7. Kracke, R. R., and Garver, H.: Differential Diagnosis of the Leukemic States, with Particular Reference to the Immature Cell Types, J. A. M. A. **104**: 697 (March 2) 1935.

8. Reich, C.: Case of Monocytoid Myeloblastic Leukemia, New York State J. Med. **32**:1193 (Oct. 15) 1932.

9. Fontana, A.: A proposito della leucemia monocitica, Minerva med. **2**:673 (Nov. 17) 1932.

10. Farrar, G. E., Jr., and Cameron, J. D.: Monocytic Leukemia with Data on the Individuality and Development of the Monocyte, Am. J. M. Sc. **184**:763, 1932.

11. Forkner, C. E.: (*a*) Material from Lymph Nodes: IV. The Heterology of Lymphoid Tissue with Special Reference to the Monocyte; Supravital Studies, J. Exper. Med. **49**:323, 1929; (*b*) The Origin of Monocytes in Certain Lymph Nodes and Their Genetic Relation to Other Connective Tissue Cells, ibid. **52**:385, 1930.

12. Doan, C. A., and Wiseman, B. K.: The Monocyte, Monocytosis and Monocytic Leukosis, Ann. Int. Med. **8**:383, 1934.

their views. Let it suffice to say that relatively recent studies, particularly those of Sabin and her associates, have given overwhelming evidence to support the theory of the existence of monocytes as an independent strain of cells. I [13] have presented clinical, hematologic and histologic evidence which indicates that acute monocytic leukemia usually is characterized by a syndrome which differs from that of other forms of acute leukemia.

Still another source of confusion is in the terminology relating to monocytes. They have been designated by some workers as transitional cells, large mononuclear leukocytes, blood histiocytes or endothelial leukocytes. Some authors have failed to appreciate the distinction between the so-called blood histiocytes and the hemohistioblasts of Ferrata. Hence, several papers refer to cases of hemohistioblastic leukemia, although it is obvious from the text that monocytic leukemia is meant. Osgood and Lyght [14] apparently used stem cell leukemia and monocytic leukemia as synonymous terms. Dameshek [15] has confused the issue by indicating that monoblasts, hemohistioblasts, clasmatocytes, reticular cells, histiocytes and resting wandering cells are identical, an opinion which is entirely without support. Furthermore, Dameshek has stated, quite incorrectly, that the consensus is that the monocyte is derived directly from the histiocyte and has given as evidence that vital staining and supravital staining methods support this view. On the contrary, the brilliant researches of Evans and Scott,[16] of Simpson,[17] of Sabin and her associates [18] and of others using these technics have resulted in a strict separation of these two groups of cells. These misleading errors in terminology have been pointed out by Clough [19] and by Levine.[20]

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13. Forkner, C. E.: Clinical and Pathologic Differentiation of the Acute Leukemias, Arch. Int. Med. **53**:1 (Jan.) 1934.

14. Osgood, C.. W., and Lyght, C. E.: Monocytic Leukemia, J. Lab. & Clin. Med. **18**:612, 1933.

15. Dameshek, W.: Acute Monocytic (Histiocytic) Leukemia, Arch. Int. Med. **46**:718 (Oct.) 1930.

16. Evans, H. M., and Scott, K. J.: On the Differential Reaction to Vital Dyes Exhibited by the Two Great Groups of Connective Tissue Cells, Contrib. Embryol. **10**:1, 1921.

17. Simpson, M. E.: The Experimental Production of Macrophages in the Circulating Blood, J. M. Research **43**:77, 1922.

18. Sabin, F. R.; Doan, C. A., and Cunningham, R. S.: Discrimination of Two Types of Phagocytic Cells in the Connective Tissues by the Supravital Technique, Contrib. Embryol. **16**:125, 1925.

19. Clough, P. W.: Monocytic Leukemia, Bull. Johns Hopkins Hosp. **51**:148, 1932.

20. Levine, V.: Monocytic Leukemia: Report of Nine Cases, Folia haemat. **52**:305, 1934.

A number of authors have used the terms reticulosis and reticulo-endotheliosis as synonyms for monocytic leukemia. The term aleukemic reticulosis was used by Letterer [21] to designate a condition in which there was general systemic hyperplasia of the endothelium of the blood vessels of the hematopoietic organs but no leukemic blood picture. Ewald [22] observed a case of acute leukemia, probably monocytic in type, which he labeled leukemic reticulo-endotheliosis. Griffin and Watkins [23] discussed cases of so called subleukemic splenic reticulo-endotheliosis. Böhne and Huismans [24] and Dameshek [25] have reviewed the subject of reticulosis and aleukemic reticulosis. Dameshek found thirteen acceptable reports of cases of aleukemic reticulosis in the literature and suggested that the condition is a distinct entity related to monocytic leukemia in the same way that subleukemic lymphogenous leukemia and subleukemic myelogenous leukemia are related respectively to lymphogenous leukemia and myelogenous leukemia. Dameshek's patient had recurrent bouts of fever and progressive weakness which terminated after six months in death. On physical examination at first nothing abnormal was noted. Later a lymph node in the neck became slightly enlarged, and subsequently the spleen became palpable. During observation there occurred fever of the typical Pel-Ebstein type. Anemia, thrombopenia and leukopenia were marked, but there were normal proportions of the various blood cells. Biopsy of the bone marrow and postmortem observations revealed a proliferation of reticulo-endothelial cells in the lymph nodes, spleen, bone marrow, liver and other organs. Reticulin fibers were demonstrated easily in the pathologic tissues. Giant cells of the Sternberg-Reed type were numerous. Rare eosinophils were present.

I can find no reason for regarding these conditions as due to reticulo-endothelioses, unless one wishes to change the whole nomenclature of the diseases ordinarily regarded as lymphoblastomas. Dameshek has not made it clear whether he regarded the disease as a lesion of the cells of the reticular syncytium or as a lesion of those cells commonly called macrophages (histiocytes or clasmatocytes) which are differentiated toward more definite types with a function of

21. Letterer, E.: Aleukämische Retikulose, Frankfurt. Ztschr. f. Path. **30**:377, 1924.

22. Ewald, O.: Die leukämische Reticuloendotheliose, Deutsches Arch. f. klin. Med. **142**:222, 1923.

23. Giffin, H. Z., and Watkins, C. H.: Distinction Between Splenic Anemia and Subleukemic Splenic Reticulo-Endotheliosis, Am. J. M. Sc. **188**:761, 1934.

24. Böhne, C., and Huismans, L.: Beiträge zur Kenntnis der chronischen leukämischen Reticuloendotheliosen, Virchows Arch. f. path. Anat. **283**:575, 1932.

25. Dameshek, W.: Proliferative Diseases of the Reticulo-Endothelial System: II. Aleukemic Reticulosis, Folia haemat. **49**:64, 1933.

phagocytosis. No adequate reason was given for not classifying the condition as lymphoblastoma of the Hodgkin type, as was done by Krumbhaar [26] in a similar case. In certain instances in which the lesions are not so typical of Hodgkin's disease the condition may be more appropriately termed reticulum cell sarcoma. If the cells do indeed meet the description of those of the monocyte series, then monoblastoma would be an appropriate term.

The terms aleukemic and leukemic reticulosis have been used to designate monocytic leukemia because some authors believe in the theory that monocytes have their origin from the reticulo-endothelial system. These terms have been used repeatedly by a considerable number of writers, notwithstanding the fact that there exists no clear-cut evidence to indicate that monocytes are related in any intimate way with the reticulo-endothelial system considered in its strict sense. I [11b] have demonstrated that monocytes do not react specifically to the agents used for demonstrating the reticulo-endothelial system and that they therefore must be considered as independent of the system.

From the histologic point of view it appears to be as proper to regard lymphocytic or neutrophilocytic leukemia or any other type of leukemia as an example of reticulo-endotheliosis, although to do so is meaningless. Hodgkin's disease, Kaposi's disease, Gaucher's disease and hyperplasia of the macrophages in the blood-forming organs as the result of infection have been designated by various workers as reticulosis or reticulo-endotheliosis of one or another sort. The terms reticulosis and reticulo-endotheliosis as synonyms for monocytic leukemia add nothing but confusion to the subject and cannot be acceptable to the large group of workers who do not accept the view that monocytes arise from macrophages (reticulo-endothelial cells).

Krahn [27] and Akiba [28] said that they believed that the conditions called leukemic and subleukemic reticulo-endotheliosis are not true leukemia but the result of general systemic infection.

TERMINOLOGY OF SUBLEUKEMIC (ALEUKEMIC) LEUKEMIA, PSEUDO-LEUKEMIA, LEUKANEMIA AND RELATED STATES

Leukemia is a disease which exhibits manifold characteristics both clinically and histologically. It may be shown eventually that the con-

26. Krumbhaar, E. B.: Hodgkin's Disease of Bone Marrow and Spleen Without Apparent Involvement of Lymph Nodes, Am. J. M. Sc. **182**:764, 1931.

27. Krahn, H..: Reticuloendotheliale Reaktion oder "Reticuloendotheliose," Deutsches Arch. f. klin. Med. **152**:179, 1926.

28. Akiba, R.: Ueber Wucherung der Retikulo-Endothelien in Milz- und Lymphknoten und ihre Beziehung zu den leukämischen Erkrankungen, Virchows Arch. f. path. Anat. **260**:262, 1926.

ditions which today are regarded as various types of leukemia are a heterogeneous group of diseases. It is well established that in some cases of leukemia there is no significant change in the total number of leukocytes in the blood throughout the course of the disease, and in other cases there may be leukopenia throughout and that in many cases at different periods in the disease there is a characteristic decreased, normal or increased number of cells, whereas in the majority of cases there is a marked increase in the total number of leukocytes in the blood throughout the course of the illness. Furthermore, it is established, almost without exception if careful qualitative studies of the blood are made, that immature leukocytes, often in significant numbers, are demonstrable in the blood and that there is a disproportion in the kinds of leukocytes, even though there may be a decrease or no increase in their total number in the blood.

The physician not thoroughly familiar with the field of hematology will find the group of diseases included in this subgroup most confusing. Obviously there is much need for a simplified concept of these processes based on a fundamental principle, so as not to allow the subject to be confused by an endless combination of terms proposed by those who report cases. Although the use of the expression aleukemic leukemia implies that there are no immature cells in the blood but that leukemia is present as demonstrated by other means, this has not been the usual interpretation of the process. Frequently the term has been used interchangeably and synonymously with pseudoleukemia, and it is therefore open to the same criticism. A variety of clinical conditions have been called aleukemic leukemia. Chief among this group are leukemic states in which there is either temporary or persistent failure of the proliferating immature cells to enter into or to remain in the blood stream. Many workers have objected to the term aleukemic leukemia on the basis that it is a contradiction of terms. It seems appropriate to avoid this contradiction by the substitution of the term subleukemic leukemia.

Is it possible to formulate any organized concept of the disease states variously referred to as pseudoleukemia, anemia pseudoleukaemica, pseudoleukanemia, splenic pseudoleukemia, aleukemic leukemia, aleukemic leukosis, aleukemic lymphatic leukemia, aleukemic myelogenous leukemia, aleukemic lymphadenosis, aleukemic myelosis, aleukemic reticulosis, aleukemic reticulo-endotheliosis, aleukemia, aleukia, aleukemic erythroblastosis, aleukocythemic leukemia, medullary leukemia, aplastic leukemia, anemoleukemia, leukanemia, subleukemic leukemia, leukopenic leukemia or lymphoblastoma aleukaemicum? This is not a mere list of names that have been invented but a list of terms which have been used by various physicians. Furthermore, I have not listed all, merely some of those terms which have been employed repeatedly. All com-

binations of these terms have been used by various writers, each basing his classification or terminology on some clinical, histologic or other characteristic of the disease studied. As previously stated, it is logical and practicable to divide all the instances of leukemia with regard to acute and chronic forms and further with regard to leukemic and subleukemic varieties (table 2), the latter term indicating whether or not an increased number of leukocytes is present in the blood. Further separation is made depending on the type of cell involved in the leukemic process. Thus a simple classification is evolved which encompasses all the types of leukemia encountered and is devoid of the heterogeneous terms which add confusion. For the sake of clearness some of the commonly used terms will be discussed, mostly for the purpose of indicating their shortcomings and of orienting the reader of the medical literature on the subject.

Soon after Virchow [2] described lymphocytic leukemia, Cohnheim [29] recorded a case in which the tissue presented identical anatomic characteristics but the blood did not show an increase in the proportion of white and red corpuscles. He proposed the term pseudoleukemia to designate this picture. It should be remembered that the study of Cohnheim was made prior to the use of apparatus for the direct enumeration of blood cells and prior to the development of methods giving clear differentiation of the ages and types of leukocytes. Since the publication of this original work the term pseudoleukemia has been applied, often indiscriminately, to a large variety of conditions, including subleukemic lymphogenous or myelogenous leukemia, lymphosarcoma, lymphogranuloma (Hodgkin's disease), xanthoma (Schüller-Christian's disease), Niemann-Pick's disease, Gaucher's disease, enlargement of the lymph nodes associated with infections and various other obscure diseases having certain characteristics suggesting leukemia.

Ebstein [30] described cases of acute pseudoleukemia, and Pinkus [31] observed that in the pseudoleukemia of Cohnheim there was a relative increase in the number of lymphocytes in the blood, often with the presence of immature cells.

The term pseudoleukemia is an unfortunate one, in that it has been used not only to include cases like those of Cohnheim, Pinkus and others but more or less as a scrap basket for various atypical pictures

29. Cohnheim: Ein Fall von Pseudoleukämie, Virchows Arch. f. path. Anat. **33**:451, 1865.

30. Ebstein, W.: Ueber die akute Leukämie und Pseudoleukämie, Deutsches Arch. f. klin. Med. **44**:343, 1888-1889.

31. Pinkus, F., in Nothnagel, C.: Specielle Pathologie und Therapie, Vienna, A. Hölder, 1901, vol. 8, pt. 1; cited by Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

simulating, in one way or another, leukemia. Naegeli,[32] for example, under the heading pseudoleukemia included the following subheads:

A. Lymphocytomas
   1. Aleukemic lymphadenosis (true pseudoleukemia)
   2. Lymphosarcomatosis (Kundrat)
   3. Localized lymphosarcoma

B. Myelosis
   1. Aleukemic myelosis

C. Granulomas
   1. Lymphogranuloma (Paltauf)
   2. Tuberculous granuloma
   3. Syphilitic granuloma
   4. Leprous granuloma

D. Splenic pseudoleukemia, with isolated enlarged spleen

E. Myelogenous pseudoleukemia (myeloma)

Obviously it is no longer possible to speak of pseudoleukemia in any strict sense of the word, and the term is becoming unpopular in hematologic literature.

Von Jaksch[33] described the blood picture that is sometimes seen in anemic infants and with which his name has been associated (von Jaksch's anemia, anemia pseudoleukaemica infantum, secondary infective myelemia of infancy, rachitic myelemia, splenic anemia of infancy or pseudoleukaemia infectiva). The young child usually has a large spleen, severe chronic anemia, a low color index, leukocytosis and a variable number of immature leukocytes, megaloblasts and normoblasts in the blood. Infection and undernutrition are the most common causes of this syndrome. It is undoubted, however, that a number of different clinical entities have in the past been included under this heading. Among these, in addition to infection and undernutrition, may be mentioned erythroblastic anemia, hemolytic jaundice, subleukemic leukemia and Banti's syndrome. The term von Jaksch's anemia and its various equivalents have, for the most part, been discarded in favor of more precise expressions.

Since Hirschfeld[34] pointed out the existence of subleukemic myelogenous leukemia (aleukemic myelosis) a large number of cases

32. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931.

33. von Jaksch, R.: Ueber Leukämie und Leukocytose im Kindesalter, Wien. klin. Wchnschr. **2**:435, 1889.

34. Hirschfeld, H.: Die generalisierte aleukämische Myelose und ihre Stellung im System der leukämischen Erkrankungen, Ztschr. f. klin. Med. **80**:126, 1914.

have been reported, and there has been a tendency to create a clinical entity. Jaffé [35] reviewed the subject but proposed to restrict the term to those conditions in which there is no leukocytosis and in which no immature cells are encountered at any time in the blood. Under these conditions subleukemic myelogenous leukemia would be an exceedingly rare disease, and the diagnosis would rest almost entirely with the pathologist. Such restriction seems hardly justifiable on the basis of existing knowledge. Most writers have designated myelogenous leukemia, either acute or chronic, in which there is no increase in the total leukocytes of the blood as aleukemic or subleukemic myelogenous leukemia. In many of the cases reported there have been varying numbers of myelocytes and myeloblasts in the blood. In some of these cases large numbers of nucleated red blood corpuscles have been present in the blood, and extensive erythropoiesis has been observed in the tissues. In every respect, except for the blood picture, subleukemic myelogenous leukemia may be identical with the leukemic form of the disease. Cases of acute involvement in which there is no qualitative or little quantitative change in the leukocytes may be confused easily with cases of thrombocytopenic purpura haemorrhagica or with aplastic anemia, whereas in the analogous cases of chronic involvement the clinical picture is similar to that of early Banti's syndrome. Stephens and Bredeck [36] discussed the relation of aleukemic myelosis to osteosclerosis. Baldridge and Fowler [37] reported on ten cases and discussed at length the clinical features of the disease.

Subleukemic lymphogenous leukemia (aleukemic lymphogenous leukemia or aleukemic lymphadenosis) is a disease state in which there is lymphogenous leukemia without an increase in the leukocyte count, although there may be any degree of alteration qualitatively in the leukocytes. The term aleukemic as a modifier of the term leukemia has invited the inclusion of a host of diseases into this category. In many of the cases reported there was only a superficial resemblance to leukemia. Subleukemic lymphogenous leukemia should include only those conditions in which the diagnosis of leukemia is established and in which the total leukocyte count is not significantly elevated. Obviously in many of the cases there will eventually be shown a frank leukemic blood picture. No essential difference histologically has been shown to exist in the tissues in subleukemic lymphogenous leukemia and frank leukemic lymphogenous leukemia. Theories relative to the reasons why

35. Jaffé, R. H.: Aleukemic Myelosis, Arch. Path. **3**:56 (Jan.) 1927.

36. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087, 1933.

37. Baldridge, C. W., and Fowler, W. M.: Aleukemic Myelosis, Arch. Int. Med. **52**:852 (Dec.) 1933.

some conditions remain subleukemic and others are frankly leukemic have been discussed elsewhere.[38] In the literature there is no clear distinction between conditions regarded by some authors as subleukemic (aleukemic) lymphogenous leukemia and by others as pseudoleukemia of the lymphogenous type.

A number of papers have been written in recent years referring to cases of so-called aplastic leukemia or to cases of leukemia in which the clinical picture has simulated closely that of aplastic anemia. Abt [39] and Baar [40] pointed out the frequency with which subleukemic leukemia in children is confused with aplastic anemia, the latter disease being much the rarer of the two. Akerrén [41] recorded the case of a 4 year old boy who had pain in the region of the hip joint, pallor, emaciation and weakness. Three months after the onset he showed profound anemia with leukopenia, lymphocytes predominating, and thrombopenia. There was no enlargement of lymph nodes, spleen or liver until five months after the onset. Hemorrhagic phenomena appeared, and the child died seven months after the appearance of the first symptoms. Postmortem examination showed typical lymphogenous leukemia. It was pointed out in the discussion that in some cases of leukemia in childhood the onset is characterized by more or less marked anemia of the aplastic type, without an increase in the number of abnormal types of lymphocytes and without enlargement of the liver, spleen or lymph nodes. Livingstone [42] and Weber [43] each studied an adult in whom the condition closely simulated aplastic anemia, but at autopsy it proved to be subleukemic lymphogenous leukemia (aleukemic lymphadenosis) in the first and subleukemic myelogenous leukemia (aleukemic myelosis) in the second case. Weber and Weisswange [44] studied a similar case in a boy of 11 years. At the beginning of the illness the picture simulated that of aplastic anemia. Autopsy demonstrated lymphocytic infiltration, especially of the kidneys, liver, testes, bone marrow and

38. Forkner, C. E.: Leukemia and Allied Disorders, to be published.

39. Abt, I. A.: Case of Aleukemic Leukemia with Clinical Symptoms of Plastic Anemia, M. Clin. North America **8**:427, 1924.

40. Baar, H.: Ueber akute aleukozytämische Leukämie im Kindesalter, Jahrb. f. Kinderh. **54**:1, 1924.

41. Akerrén, Y.: Zur Diagnose und Differentialdiagnose der Lymphadenose, besonders im Kindesalter, Acta pædiat. **13**:501, 1932.

42. Livingstone, J. L.: Lymphatic Leukemia Simulating Aplastic Anaemia, Proc. Roy. Soc. Med. **25**:1400, 1932.

43. Weber, F. P.: Aleukemic Myelosis of the Leucopenic Type, Clinically Simulating Chronic Aplastic Anemia, Quart. J. Med. **1**:409, 1932.

44. Weber, F. P., and Weisswange, W.: Lymphadenosis Commencing with the Clinical Picture of Hypoplastic Anaemia, Proc. Roy. Soc. Med. **26**:1012, 1933; Aplastische Anämie und Leukämie, Deutsches Arch. f. klin. Med. **176**:422, 1934.

lymph nodes. Zypkin [45] said he believed that aplastic anemia may be present in the terminal stage of leukemia, and Mallory [46] referred to a case of leukemia, proved at biopsy of the bone marrow, in which autopsy revealed a totally aplastic marrow.

Von Leube [47] described a rapidly progressive disorder characterized by changes in the blood which suggested pernicious anemia combined with myelogenous leukemia. Severe anemia, a high color index and the presence of excessive numbers of nucleated red corpuscles and of large immature leukocytes in the blood were noted. The author said he believed that this syndrome, which was called leukanemia, is an independent disease not included in the same category with either pernicious anemia or leukemia.

Drysdale [48] and Symmers [49] reviewed the earlier literature and reported additional cases. Symmers gave as his conclusion that leukanemia is characterized clinically by an extremely rapid course and by changes in the blood, bone marrow, spleen, liver and lymph nodes that partake of the nature of both pernicious anemia and myelogenous leukemia. He said he considered leukanemia not as an independent disease but as one of a group of rapidly progressive derangements of the blood-forming tissues due to infection.

Pinkerton [50] described a case of acute aleukemic erythroblastosis which may be regarded as a case of leukanemia. Müller and Werthemann [51] rightly pointed out that the term leukanemia is purely descriptive and should not be regarded as indicating a distinct entity. They noted that the signs referred to as characteristic of leukanemia have been observed in cases of acute myelogenous leukemia, nitrobenzene poisoning, pernicious anemia, anemia following roentgen irradiation, lymphosarcomatosis, malaria, sepsis and metastatic carcinoma involving bone marrow.

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45. Zypkin, S. M.: Ueber aplastische Leukanämie, Virchows Arch. f. path. Anat. **258**:600, 1925.

46. Lymphoblastoma, ? Giant Follicular Type, with Involvement of Spleen, Kidney, Bone Marrow and Lymph Glands, Cabot Case 21281, New England J. Med. **213**:67 (July 11) 1935.

47. von Leube, W.: Rapid verlaufende schwere Anämie mit gleichzeitiger leukämischer Veränderung des Blutbildes, Berl. klin. Wchnschr. **37**:851, 1900.

48. Drysdale, J. H.: Leukanaemia: Its Relation to Leukaemia and Pernicious Anemia, Quart, J. Med. **1**:89, 1907-1908.

49. Symmers, D.: Leukanemia, J. A. M. A. **76**:156 (Jan. 15) 1921.

50. Pinkerton, H.: Aleukemic Leukemia and Atypical Leukemoid Conditions: Report of Seven Cases Including One of Acute Erythroblastosis, Arch. Path. **7**:567 (April) 1929.

51. Müller, A., and Werthemann, A.: Unter dem Bilde der sog. Leukanämie verlaufende Karzinose des Knochenmarkes bei kleinem, verstektem Mammakarzinom, Folia haemat. **46**:429, 1932.

That in myelogenous leukemia at times, particularly immediately subsequent to treatment, there may be a large number of nucleated red corpuscles in the blood is within the experience of all who have observed any significant number of cases. Beiglböck [52] and many others have reported cases of this type and have discussed the relation of the picture to the syndrome of leukanemia.

SUMMARY AND CONCLUSIONS

The confusion existing in the classification and terminology of diseases of the blood-forming organs, particularly of leukemia and related disorders, is reviewed and discussed.

A classification (table 2) is presented which encompasses all known variants of leukemia and which simplifies the concepts of these disorders.

52. Beiglböck, W.: Subleukämische Myelose mit dem klinischen Bild einer perniziösen Anämie (Ein Beitrag zur Frage der sogenannten Leukanämie), Wien. klin. Wchnschr. **47**:962 (Aug. 3) 1934.

SHOCK SYNDROME IN THERAPEUTIC HYPERPYREXIA

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Studies of severe reactions in hyperpyrexia are highly suggestive of shock, and it is the thesis of this paper that the severer reactions are actually true shock. Although there have been numerous investigations into the theory of shock, no one theory has been adduced that is satisfactory to all workers in this field. Recent studies, however, have stressed the importance of a diminished volume of blood and an increased vascular permeability in the production of the shock syndrome.[1] In fact, Moon [1b] has defined shock as "the disparity between the volume of blood and the volume-capacity of the vascular system." He has stated that shock may result either from loss of blood or fluid or from atony or dilatation of the vascular walls, especially of the capillaries and venules, combinations of these two factors being the rule. According to this concept, increased capillary permeability, with leakage of plasma through the vascular walls, occurs as a result of stasis and anoxemia, still further diminishing the volume of blood.

A workable division of the types of shock or acute failure of the circulation into five groups has been offered by Blalock: [1a]

1. The hematogenic type—brought on by hemorrhage or rapid severe dehydration (burns, muscle and intestinal trauma) resulting in a diminution of blood volume and an increase of capillary permeability

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From the Boston Psychopathic Hospital.

1. (*a*) Blalock, A.: Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, Surg., Gynec. & Obst. **58**:551 (March) 1934. (*b*) Moon, V. H.: Shock Syndrome in Medicine and Surgery, Ann. Int. Med. **8**:1633 (June) 1935. (*c*) Mann, F. C., and Essex, H. E.: Present Status of the Problem of Traumatic Shock, Am. J. Surg. **28**:160 (April) 1935. (*d*) Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1935, pp. 17-27.

2. The neurogenic type—brought on by stimuli acting through the nervous system (spinal anesthesia, a blow in the solar plexus, a bullet shot) resulting in vasodilation, an increase in capillary permeability and then a diminution of blood volume
3. The vasogenic type—vascular dilation brought on by agents acting directly on the vascular walls (histamine, anaphylactic shock) leading to increased vascular permeability and hemoconcentration
4. The cardiogenic type—occurring in conditions in which there is sudden and widespread damage of the cardiac muscle (coronary thrombosis, acute diphtheritic myocarditis, prolonged tachycardia) (venous distention occurs in this group)
5. Unclassified types—the mechanism not being clear, possibly involving several factors (postoperative shock, severe acute infections, acute surgical emergencies, ether anesthesia)

Shock with peripheral vascular failure occurs in many conditions in addition to those just mentioned, such as intestinal obstruction, acute adrenal insufficiency, cholera, diabetic coma, poisoning and fatal exposure to cold.[2] The clinical picture of heat prostration is suggestive of the shock syndrome.[2a] In many conditions of shock there is not only a loss of fluid, with a reduction in the blood volume, but a loss of considerable salt from the body (intestinal obstruction, diabetic coma, acute adrenal insufficiency and other conditions [3]). The pathologic picture is the same in many of these conditions and is typical of the shock syndrome.[1b]

Experience in this clinic has shown that in therapeutic hyperpyrexia induced by hot moist air, as in the Kettering hypertherm, a clinical picture of shock is occasionally seen at temperatures of about 106 F. or above. An opportunity has thus been afforded to make clinical and laboratory observations on patients reacting in this manner to hyperpyrexia.

STUDY

Methods of Induction of Fever.—Fever is induced by means of the Kettering hypertherm. The patient, during fasting, lies in an insulated cabinet and is exposed to a current of hot moist air of a fixed velocity and with a humidity of from 35 to 50 per cent. The level of the dry bulb temperature ranges from 155 to 160 F.; the level of the wet bulb temperature from 130 to 135 F. The body of the patient is first bathed with liquid petrolatum and then covered with terry cloth towels to prevent cutaneous burns. The head protrudes from the cabinet and is cooled with an electric fan. The body temperature is raised to levels of 104 and 106 F.

2. (*a*) Atchley, D. W.: Role of Peripheral Circulatory Failure in Clinical Medicine, New England J. Med. **213**:861 (Oct. 31) 1935. (*b*) Harkins, H. N.: Shock Due to Freezing: Shift of Body Fluids and Associated Blood Concentration Changes, Proc. Soc. Exper. Biol. & Med. **32**:432 (Dec.) 1934. (*c*) Blalock.[1a] Moon.[1b] Mann and Essex.[1c] Harrison.[1d]

3. Moon.[1b] Atchley.[2a]

(rectal), depending on the condition treated, these levels being reached usually in from sixty to ninety minutes. The current of hot moist air is then turned off, and the patient is covered with woolen blankets to prolong the increased body temperature as long as desired, usually for from three to five hours. Six-tenths per cent saline solution is given by mouth as desired, and an attempt is made to reach an intake of from 1,000 to 1,200 cc. during the first ninety minutes, the total intake being about 3 or 4 liters during a five hour prolongation of temperature. Treatment is given once a week.

Subjects.—Artificial fever therapy has been given to patients with ages ranging from 6 to 60 years. The contraindications to this type of treatment are few and include marked hypertension, active pulmonary tuberculosis, acute nephritis, marked debility and myocardial failure. There are persons, however, who though in good physical condition cannot be given artificial fever by means of the hypertherm because of an inability to tolerate the high wet and dry bulb temperatures of the environmental blanket of air. It is in these persons especially that severe reactions are most likely to occur.

RESULTS

Shock Reactions.—Severe reactions, considered as shock, occurred in eight patients with ages ranging from 19 to 56 years, and death resulted in two of this group.

An analysis of the data, as given in the accompanying table, reveals that the reactions occurred at temperatures of 106 F. or above, the body temperature usually showing some further rise during the reaction. In all patients an attempt was being made to prolong the body temperature at a level close to 106 F., in five patients (M. F., M. L., S. M., J. P. and D. T.) by shutting off the air current and covering the body with woolen blankets and in three patients (G. G., P. M. and A. Y.) by continuous exposure to the current of hot moist air.

The impending shock was ushered in by a sudden increase in the pulse rate, pallor or cyanosis of the skin, a continued or rapid rise in the body temperature, fluttering of the eyelids, twitchings of muscles of the face or extremities, vomiting or sudden quietness, suggesting coma in a patient who had previously complained bitterly of the heat.

Readings of the blood pressure when obtained at this time showed low levels (68 systolic and 48 diastolic; 60 systolic and 54 diastolic; 60 systolic and 30 diastolic), and in three patients the radial pulse was either weak or absent. The pulse rate at the onset was usually rapid, from 120 to 164 per minute, and in one patient (S. M.) it increased from 130 to 180.

In six patients these initial symptoms were followed by clonic or tonic convulsive movements of the jaw, extremities or trunk, and in five of the latter group the rigidity, either localized or generalized, was so marked that it was difficult to differentiate it from the tonic state of a convulsive seizure or muscle rigors due to heat cramps.[4] In one patient

4. Talbott, J. H.: Heat Cramps, Medicine **14**:323 (Sept.) 1935.

Patient, Age and Sex	Treatment No.	Diagnosis	Temperature, Pulse Rate and Blood Pressure: At Start of Treatment	Temperature, Pulse Rate and Blood Pressure: At Time of Reaction	Time of Reaction	Intake of Fluids (0.6% Saline Solution), Cc.	Vomiting	Diarrhea
M. F. 19 F	2	Juvenile dementia paralytica; rheumatic heart disease; mitral stenosis	98.2 132 106/70	106.0 164 Pulse weak	1¾ hr. after onset of treatment; current off 1½ hr. after start of treatment at temperature of 105.6 F. and pulse rate of 144; temperature prolonged for 15 min. at 105.6 to 106 F.	First hr... 800 Second hr. 400 Total.....1,200	Large amounts; total of more than 1 L. at onset of reaction	Some at onset of reaction
A. Y. 33 F	5	Dementia paralytica	99.0 100 100/60	106.0 132	2 hr. and 20 min. after start of treatment; current on during entire period; temperature prolonged for 1 hr. at 106 to 107 F.	First hr... 600 Second hr. 600 Total.....1,200	15 min. before onset of reaction; projectile; also during reaction; large amounts, as much at 1 L. at one time	.....
S. M. 36 M	9	Dementia paralytica	98.4 76 120/80	106.8 rose to 107.4 130 rose to 180 60/54	1½ hr. after start of treatment; current off 1¼ hr. after the start of treatment at temperature of 106.8 F. and pulse rate of 146; temperature prolonged for 15 min. at 106.8 F.	First hr... 600 Second hr. 200 Total..... 800	After onset of reaction; foul vomitus for next 48 hr.	24 hr. after reactions; foul diarrhea persisting for 48 hr.
J. P. 40 M	1	Acute gonorrheal urethritis	98.4 51 100/60	107.8 142	2¾ hr. after start of treatment; current off 2 hr. after start of treatment at temperature of 107 F. and pulse rate of 140; temperature rose to 107.8 F. in 45 min.	First hr... 300 Second hr. 800 Third hr... 200 Total.....1,300	Large amount of dark brown material, 1 hr. after onset of reaction; some vomiting 5 hr. after onset	Some diarrhea 1 hr. after onset of reaction
M. L. 45 M	6	Primary atrophy of optic nerve	98.2 76 140/90	107.4 156 68/48	1¾ hr. after start of treatment; current off 1¼ hr. after start of treatment at temperature of 105.4 F. and pulse rate of 132; temperature rose to 107.4 F. in ½ hr.	First hr...1,000 Second hr. 400 Total.....1,400	Considerable vomiting 1 hr. after onset of reaction	Foul; occurred about 1 hr. after onset of reaction
G. G. 49 M	1	Tabes dorsalis; atrophy of optic nerve	98.6 78	106.2 160 Pulse very weak; pressure not obtainable	1½ hr. after start of treatment; current on during entire period; temperature prolonged for ½ hr. from 106 to 106.4 F.; pulse rate rose from 118 to 160	First hr... 200 Second hr. 0 Total..... 200	1½ hr. after reaction; vomitus dark brown, with fecal odor	Occurred 1½ hr. after onset of reaction and until death; stool "reddish"
P. M. 51 M	10	Dementia paralytica	98.4 76 108/78	106.6 120 Pulse weak	2 hr. after start of treatment; current on during entire period; temperature prolonged for ½ hr. at 106 to 106.6 F.	First hr... 400 Second hr. 100 Total..... 500	Large amount, consisting of most of fluids taken; ½ hr. before onset of reaction	Occurred 24 hr. after onset of reaction; foul; persisted for 48 hr.
D. T. 56 F	5	Dementia paralytica; diabetes mellitus; chronic bronchitis	98.6 90 130/70	106.7 rose to 107 155 60/30	1¼ hr. after start of treatment; current off 1 hr. after onset of treatment at temperature of 106 F. and pulse rate of 142; temperature prolonged for ¼ hr. from 106 to 106.6 F.	First hr... 800 Second hr. 0 Total..... 800	5 hr. after onset of reaction vomited large amount of dark brown material with foul odor	Occurred 5 hr. after start of reaction; foul

Tremors, Twitchings, Convulsions	Delirium and Coma	Excitement	Cough	Drugs	Course and Treatment	Other Data
Twitchings of muscles of face, feet and hands; fluttering of eyelids followed by generalized convulsion	Delirium	Considerable jactitation	.....	.....	Intravenous infusion of 600 cc. of 0.9% saline and 5% dextrose solution; convulsions ceased after infusion; patient well after 1 hr.	.....
Quivering of eyelids and twitchings of muscles of upper extremities at onset of reaction; reflexes increased	Delirium	Hyperactive	.....	Sodium amytal, 3 grains at start of treatment	Calcium gluconate intramuscularly gave no relief for muscle tremors; fluids by mouth caused vomiting; intravenous infusion impossible because of poor condition of veins; hypodermoclysis of 2,000 cc. of 0.9% saline and 3% dextrose solution; patient recovered in 1¾ hr.	.....
Fluttering of lids; twitchings of facial muscles; involuntary movements of fingers 1½ hr. after onset of reaction, followed by repeated generalized convulsions for 4 hr.; loss of control of vesical and rectal sphincters	Coma	Maniacal; considerable jactitation	.....	.....	Intravenous infusion of 750 cc. and then 500 cc. of 0.9% saline and 4% dextrose solution; caffeine with sodium benzoate subcutaneously; ether, 4 cc., intramuscularly; soluble phenobarbital U.S.P (sodium phenobarbital) in repeated doses, 22 grains intramuscularly for convulsions; stormy convalescence of 8 wk.	Subnormal temperature for 3 days; marked icterus; pyuria, with very high nonprotein nitrogen content; thrombophlebitis of thighs; bronchopneumonia; sepsis; polyneuritis; severe anemia
Clonic movements of jaw and extremities at start followed by rigidity of extremities and trunk and spasms of abdominal muscles; loss of control of vesical and rectal sphincters	Delirium	Considerable jactitation, made worse by application of ice to skin	.....	Sodium amytal, 3 grains, ¾ hr. after start of treatment	Intravenous infusions of 0.9% saline and 5 and 10% dextrose solution; three bromides N. F., 30 grains (2 Gm.), by rectum for excitement; recovered in 24 hr.	Respirations during reaction irregular and slow, with apnea and hyperpnea
Clonic movements of left hand 1 hr. after onset of reaction; loss of control of rectal sphincter	Delirium followed by coma	Maniacal and very hyperactive	.....	.....	Intravenous infusion of 650 cc. of 0.9% saline and 8% dextrose solution; recovered in 24 hr.	Very restless during treatment; during reaction respirations slow, shallow, irregular, with periods of apnea
Generalized rigidity 1½ hr. after onset of reaction; muscle rigidity or generalized convulsion ¾ hr. before this; loss of control of vesical and rectal sphincters	Coma	Marked restlessness and hyperactivity	Considerable thick tenacious sputum and frothy mucopurulent material	Sodium amytal, 6 grains, ¼ hr. before treatment	Artificial respiration for failure of respiration; 5% carbon dioxide and oxygen, with some improvement; epinephrine and caffeine subcutaneously; calcium gluconate did not relieve convulsion; hypodermoclyses of 1,500 cc. of 0.9% saline and 2½% dextrose solution 8 and 10 hr. after reaction; morphine, ¼ grain, subcutaneously 1 hr. before death	At time of reaction: skin pale, no cyanosis; respiration slow, shallow, irregular, with long apneic periods; restlessness; lungs revealed many râles; death due to respiratory failure
Twitchings and clonic movements of jaw muscles at onset of reaction; occasional rigidity of extremities; Chvostek +; knee and ankle jerks not increased	Delirium followed by coma	Considerable hyperactivity	Cough productive of thick tenacious mucopurulent material	Sodium amytal, 3 grains, 1½ hr. after start of treatment	Intravenous infusion of 1,000 cc. of 0.9% saline and 3% dextrose solution; recovered in 2½ hr., except for weakness and diarrhea, which persisted for 48 hr.	.....
Generalized rigidity 2 hr. after onset of reaction; repeated convulsions; clonic movements of left upper extremity; paralysis of left side of face, left upper and lower extremities and right lower extremity; loss of control of vesical and rectal sphincters	Coma	Hyperactive; some jactitation	.....	Morphine, ⅛ grain, subcutaneously ¼ hr. after start of treatment	Intravenous infusion of 0.9% saline and 10% dextrose solution, 2,400 cc. in 3 hr.; epinephrine intravenously; 5% carbon dioxide and oxygen; blood pressure rose to 135/60 5 hr. after reaction; death due to respiratory paralysis	Urine contained no acetone, sugar or diacetic acid; breathing labored; nail beds cyanotic; auricular fibrillation during reaction; basal pulmonary râles; autopsy

(S. M.) repeated tonic and clonic convulsive seizures occurred over a period of four hours and resembled closely those due to strychnine poisoning and tetanus, the seizures being initiated by the slightest stimulus, such as a flash of light, a touch on the body, a jarring of the bed or the closing of a door, and being accompanied with maniacal excitement. (A similar response has been observed in patients with heat cramps, for whom a cool breeze or a sudden jarring of the bed was sufficient to throw the affected muscles into contraction.[4]) In another patient (D. T.) convulsions recurred infrequently up to the time of death. In a third patient (J. P.) spasmodic movements of the abdominal muscles occurred.

The intake of 0.6 per cent saline solution up to the time of the onset of the reaction ranged from 200 to 1,400 cc.; 200 to 1,000 cc. during the first hour and 0 to 800 cc. during the second hour. The need of a sufficient intake of fluid is increased by the vomiting and diarrhea which also occur. Vomiting occurred in all our patients before, during or after the onset of the reaction, and in some cases was considerable, an amount practically equal to the intake of fluid during the fever treatment being disgorged. The vomitus was usually foul; that of one patient (G. G.) had a fecal odor, and that of three patients was dark brown. Diarrhea, usually accompanied with a foul odor, was a prominent symptom in seven patients, occurring during the reaction and even over a period of forty-eight hours. The stool of one patient (G. G.) was reported as "reddish." In four patients loss of control of the bladder and in five patients loss of control of the rectal sphincter occurred.

In all patients considerable hyperactivity, jactitation and maniacal excitement occurred, and it was necessary to restrain them. This episode was either preceded or followed by coma or delirium or both.

In three patients (P. M., G. G. and D. T.) clinical signs of pulmonary edema were present. In the first two there was considerable coughing, productive of thick mucopurulent and tenacious sputum. In the third patient aspiration of the trachea was performed because of gurgling râles and was productive of bloody mucus, the diagnosis of pulmonary edema being verified on postmortem examination.

The skin of each patient was hot and dry. This is important, since severe reactions on exposure to a high temperature, as in heat stroke, are most likely to occur when sweating ceases.[5]

Drugs were administered to five patients of this group before or during fever therapy: to three patients, 3 grains (0.2 Gm.) of sodium amytal; to one patient, 6 grains (0.4 Gm.) of sodium amytal, and to the fifth patient, ⅙ grain (10 mg.) of morphine sulfate subcutaneously.

5. Hill, L.: The Nature, Prevention, and Treatment of Heat Hyperpyrexia: The Physiological Aspect, Brit. M. J. **1**:397 (March 20) 1920.

Six patients survived the treatment, five recovering completely in from one to forty-eight hours, with no residual findings or complaints. The sixth patient (S. M.) experienced a stormy convalescence of eight weeks, and since the course in this case and in two others (G. G., D. T.) in which death occurred are of interest, detailed protocols will be given.

REPORTS OF CASES

CASE 1.—S. M., a 42 year old man suffering from dementia paralytica, had had treatment for approximately five years consisting of three malarial paroxysms, nine periods of fever due to typhoid vaccine, twenty diathermy treatments and fifty-nine injections of tryparsamide intravenously. After temporary improvement he relapsed mentally and according to the serologic evidence. Fever was then induced by means of the Kettering hypertherm.

Physical examination of the patient indicated a lesion at the apex of the left lung, and roentgenograms corroborated this finding. Examination of the urine showed 5 leukocytes and a rare erythrocyte per high power field. Except for the neurologic signs of dementia paralytica, the examination showed no further abnormality.

One fever treatment by means of the electric blanket and eight treatments in the hypertherm over a period of eight weeks were well tolerated. The ninth fever treatment with the hypertherm was given on July 8, 1935, and although given under the same circumstances as the previous ones, led to shock. The protocol of this treatment is given in detail:

9:15 a. m.: Pulse rate, 84; temperature, 98.4 F.; blood pressure, 120 systolic and 80 diastolic; patient placed in hypertherm

10:15 a. m.: Pulse rate, 120; temperature 106.6 F.; current turned off; patient covered with woolen blankets; total intake of fluid, 600 cc. of 0.6 per cent saline solution

10:30 a. m.: Pulse rate, 146; temperature, 106.8 F.

10:45 a. m.: Pulse rate, 150; temperature, 107.2 F.; marked pallor of face; weak pulse; patient uncovered; skin rubbed with ice; fans directed at body; total intake of fluid, 800 cc. of 0.6 per cent saline solution

11:00 a. m.: Stuporous; pulse rate, 180; temperature, 107.4 F.

11:20 a. m.: Pulse rate, 180; temperature, 107.4 F.

11:53 a. m.: Pulse rate, 180; temperature, 107.4 F.; blood pressure, 60 systolic and 54 diastolic; caffeine with sodium benzoate, 7½ grains (0.5 Gm.), subcutaneously; intravenous infusion of 750 cc. of 0.9 per cent saline and 4 per cent dextrose solution started; sample of blood taken after injection of 75 cc. of fluids showed value for plasma chloride of 546 mg. per hundred cubic centimeters

12:00 m.: Blood pressure, 65 systolic

12:10 p. m.: Pulse rate, 106; temperature, 106.2 F.; blood pressure, 75 systolic and 60 diastolic; twitchings of muscles of body and fingers and about mouth; fluttering of eyelids; wide dilatation of pupils

12:18 p. m.: Blood pressure, 75 systolic and 60 diastolic; rapid, repeated, violent attacks of clonic movements of arms and legs and shrieking; marked hyperactivity; patient restrained; touching patient, flash of light, jar of bed or application of ice to body caused violent clonic movements; clysis terminated

12:30 p. m.: Convulsions continued; pulse rate, 164; temperature, 104 F.

1:00 p. m.: Convulsions continued; pulse rate, 156; temperature, 103 F.

1:00 to 2:35 p. m.: Soluble phenobarbital U. S. P. (sodium phenobarbital), 16 grains (1 Gm.) and ether, 4 cc., intramuscularly; convulsions continued

1:55 p. m.: Pulse rate, 176; temperature, 107 F.

3:00 p. m.: Pulse rate, 120; temperature, 103.6 F.; respiratory rate, 40; convulsions continued but less violent; 500 cc. of 5 per cent solution of dextrose intravenously followed by profuse perspiration; patient semicomatose

8:00 p. m.: Pulse rate, 128; temperature, 102.8 F.; respiratory rate, 36; 1,600 cc. of 5 per cent dextrose and 0.9 per cent saline solution subcutaneously

10:00 p. m.: Pulse rate, 120; temperature, 104.2 F.; respiratory rate, 26; blood pressure, 78 systolic and 68 diastolic; caffeine, 7½ grains (0.5 Gm.), subcutaneously

12:00 m.: Pulse rate, 120; temperature, 103.8 F.; respiratory rate, 26; blood pressure, 78 systolic and 68 diastolic; caffeine repeated

2:00 a. m.: Pulse rate, 140

The blood pressure remained low for twenty-four hours after the shock reaction (84 systolic and 68 diastolic). In addition, the patient had diarrhea, with foul stools. Two days after the reaction the patient was unable to retain any food by mouth, and the rectal temperature was subnormal (96 to 96.8 F.). On the third day a subicteric tint of the conjunctivae was noticed, and the patient was drowsy, apathetic and confused. Examination of the urine showed a slight trace of albumin, 20 leukocytes and many clumps of pus cells per high power field. His memory was impaired, and bilateral ankle clonus, the Gordon reflex and no abdominal reflex on the left were noted. Neurologic and mental changes had occurred as a result of the shock reaction. Because of the vomiting of food and fluids, hypodermoclyses of saline and dextrose solution were given.

The jaundice became more marked and persisted for eight days (July 11 to 19), the icteric index rising to 85. The van den Bergh test showed a delayed indirect reaction. Examination of the urine revealed no bile, slight traces of albumin and pus cells. The nonprotein nitrogen value rose to 88 mg. per hundred cubic centimeters of blood. The white cell count was as high as 26,600; the red cell count, 3,940,000, and the hemoglobin content, 90 per cent (Tallqvist). During this period cellulitis and phlebitis of both thighs occurred, possibly owing to the clyses. This was followed by bronchopneumonia and pitting edema of the ankles, legs, abdomen and sacrum. The patient's condition was poor. He was irritable and restless and took little food. Repeated catheterizations were necessary because of incontinence and distention of the bladder.

From July 20 to 31 the nonprotein nitrogen content of the blood ranged from 73 to 137 mg., the urine continued to show albumin and pus cells and the specific gravity ranged from 1.008 to 1.010. General anasarca was present. The blood pressure was 130 systolic and 60 diastolic. The heart was normal. The pulse rate varied from 100 to 115, and the temperature was normal. Irrigations of the bladder with potassium permanganate were given. Otitis media developed on the left side.

From August 1 to 15 the nonprotein nitrogen content of the blood ranged from 96 to 135 mg. A large abscess of the back developed over the upper pole of each kidney, and a decubitus developed. The anemia became more marked, the red cell count being 2,680,000, the hemoglobin value 55 per cent (Sahli) and the white cell count as high as 25,580. The blood smear revealed 86 per cent polymorphonuclear leukocytes. A Mosenthal function test of the kidneys showed fixation of the specific gravity ranging from 1.005 to 1.008, the night urine amounting to 1,850 cc. Tests showed a creatinine content of the blood of 4.95 mg., and a uric acid content of 6.1. mg. A phenolsulfonphthalein function test of the kidneys showed a total output of 27 per cent in two hours. The urine continued to show albumin and pus cells. Bilateral wrist drop developed. In view of the findings the patient was placed on a high vitamin and high caloric diet and was given iron and ammonium citrates in large doses by mouth. Improvement with this therapy was rapid and marked. The abscesses over the back healed. Within two weeks the nonprotein nitrogen content fell to 38 mg., although the urine still showed pus cells. An abscessed area which developed in the right groin was incised, and the serosanguineous material obtained was cultured and examined but with negative results. Eight weeks after the reaction the patient was sufficiently improved to be discharged. He has maintained a good mental, physical and serologic improvement.

CASE 2.—G. G., a 51 year old man, had had symptoms of tabes dorsalis for seven years. He had had a small amount of intravenous and intramuscular treatment, with no apparent benefit. On admission to the hospital he was having lancinating pains, difficulty in walking and in voiding urine and constipation. He had lost 20 pounds (9.1 Kg.). Aside from the signs of tabes dorsalis and atrophy of the optic nerve, his physical condition was good. The heart appeared normal, the pulse rate was 80 per minute and the blood pressure was 132 systolic and 88 diastolic. Several months previously he had received nine treatments with diathermy fever. On May 18, 1935, he was given his first fever treatment in the Kettering hypertherm, and this was accompanied with the shock phenomenon.

8:45 a. m.: Pulse rate, 76; temperature, 98.6 F.; patient given sodium amytal, 6 grains (0.4 Gm.); placed in hypertherm

9:45 a. m.: Pulse rate, 118; temperature, 106 F.; patient complained bitterly of heat throughout treatment

9:45 to 10:20 a. m.: Body temperature maintained at level of 106 to 106.4 F., hypertherm current remaining on; pulse rate rose from 118 to 148 in ten minutes and then to 160; intake of fluid, only 200 cc., as patient refused to drink

10:20 a. m.: Pulse rate, 160; temperature, 106.4 F.; patient in coma; suddenly ceased complaining of heat; labored respirations; no pulse obtained at wrist; patient immediately removed from cabinet; fans directed at body; body surface sprayed with lukewarm water to hasten fall in temperature

10:30 a. m.: Breathing ceased suddenly; artificial respiration started immediately; epinephrine, 8 minims (0.5 cc.), administered intravenously; pulse felt at wrist; color appeared good; caffeine with sodium benzoate, 3 grains (0.2 Gm.), given intravenously and 7½ grains (0.5 Gm.) subcutaneously; artificial respiration continued, since omission caused respirations to become more and more shallow, with cessation occurring soon

11:00 a. m.: Applications of ice to skin

11:40 a. m.: Body temperature falling; patient coughing and raising thick tenacious mucopurulent sputum; caffeine with sodium benzoate, 7½ grains (0.5 Gm.), subcutaneously

11:45 a. m.: Patient rigid; muscles of arms and legs in spasm, followed by clonic movements and cyanosis of arms; difficult to make out whether convulsive seizures or localized muscle rigors; inhalations of 5 per cent carbon dioxide and oxygen given for respiratory difficulty, with relief, respirations becoming deeper, more frequent and regular; good color of lips, ears and nails, but muscle rigidity continued

12:00 m.: No increase in reflexes; no Chvostek sign; in view of position of thumbs and fingers, tetany considered; calcium gluconate, 15 grains (0.97 Gm.), given intravenously; no relief of rigidity

12:10 p. m.: Rigidity continued; patient still in coma; stertorous breathing; restlessness; rectal incontinence; loose watery stools

2:30 p. m.: Temperature, 101.4 F.; pulse rate, 140, of fair quality

3:30 p. m.: Temperature, 101 F.; pulse rate, 95

4:00 p. m.: Temperature, 101.4 F.; pulse rate, 98; respiratory rate, 22; coma continued; paleness of skin and nail beds; coughing continued; productive of thick, tenacious, mucopurulent sputum; breath, foul; tongue, dry; only feeble first apical sound heard; blood pressure not obtainable; coarse basal râles over both lungs; no distention of abdomen; no edema of extremities; no biceps, triceps, wrist, patellar or abdominal reflexes; no Babinski sign; vesical and rectal incontinence

5:30 p. m.: Caffeine with sodium benzoate, 7½ grains (0.5 Gm.), subcutaneously; vomiting of dark brown fluid with fecal odor; thin watery bowel movements; coma continued; stertorous breathing; thick tenacious sputum

7:00 p. m.: Pulse rate, 108; respirations, 28; 1,500 cc. of 2.5 per cent dextrose and 0.9 per cent saline solution subcutaneously; patient awakened from stupor; complained of cold; hot water bottles and blankets applied; vomiting; coughing; rectal and vesical incontinence; reddish brown stools

8:20 p. m.: Temperature, 103.6 F.; pulse rate, 114; respiratory rate, 30; clysis terminated; vomiting of dark brown, watery material; repeated watery dejecta

9:00 p. m.: Complaints of pains in chest and costovertebral regions; restlessness; wanted something to put him to sleep; some fluid retained by mouth

9:30 p. m.: Pulse rate, 90; respiratory rate, 40; dozing; pulse weak; respirations shallow

10:00 p. m.: Pulse rate, 92; respiratory rate, 40; blood pressure not obtainable by auscultation; perspiration and restlessness

10:15 p. m.: Pulse rate, 90; respiratory rate, 40; complaints of shortness of breath; dozing

11:05 p. m.: Pulse rate, 90; respiratory rate, 40; poor color; perspiring, pulse of poor quality; caffeine, 7½ grains (0.5 Gm.), subcutaneously

11:25 p. m.: Morphine, ⅛ grain (8 mg.), subcutaneously for restlessness

11:35 p. m.: 1,500 cc. of 0.9 per cent saline and 2.5 per cent dextrose solution subcutaneously

11:55 p. m.: Poor color; pulse rate, 90 and weak; respiratory rate, 42 and shallow

12:00 m.: Digifoline, 3 grains (0.2 Gm.), subcutaneously; pulse rate, 88 (?)

12:14 a. m.: Pulseless

12:18 a. m.: Epinephrine, 15 minims (1 cc.), subcutaneously

12:20 a. m.: Respirations ceased; at no time during shock reaction was blood pressure obtainable

The outstanding observations in this case were vascular collapse, coma, convulsions, loss of sphincteric control, pulmonary edema, respiratory paralysis and neurologic changes as a result of the shock reaction. The respiratory distress was considerably relieved by inhalations of 5 per cent carbon dioxide and oxygen. Death was probably hastened by the injudicious use of morphine 1 hour before. Permission for a postmortem examination was not obtained.

Case 3.—D. T., a 56 year old woman, was admitted with a diagnosis of dementia paralytica,[6] diabetes mellitus and chronic bronchitis. Mental deterioration had been noticed for two months. The blood showed a positive Kahn reaction. Examination of the spinal fluid revealed a positive Wassermann reaction, 160 lymphocytes per cubic millimeter; a total protein content of 78 mg. per hundred cubic centimeters, a positive Pandy reaction and a colloidal gold reaction of 5555543210.

Examination of the patient revealed that she weighed 148 pounds (67 Kg.). The lungs were normal. The heart was not enlarged to percussion, and the sounds were of fair quality. A short harsh systolic murmur was noted at the apex and was not transmitted. The rhythm was regular. The aortic second sound was greater than the pulmonic second sound. The rate was 72. The blood pressure was 114 systolic and 68 diastolic. A scar (gallbladder operation) was noted over the upper right portion of the rectus muscle, and another scar (operation on the urinary bladder) was noted in the lower midabdominal region. The liver was felt in the right midclavicular line 2 fingerbreadths below the costal margin. The edge was smooth and thickened but not tender. The pupils were small and of an Argyll Robertson type. The knee jerks were absent, but the ankle jerks were present.

The value for blood sugar during fasting was 200 mg. The patient was receiving a diabetic diet containing 125 Gm. of carbohydrate, 50 Gm. of protein and 50 Gm. of fat, with 10, 10 and 5 units of insulin daily. A roentgenogram of the chest showed evidence of chronic bronchitis that was not noted on physical examination. The patient received four fever treatments at weekly intervals without alarming symptoms, although she complained of discomfort more than the average patient. For this reason she was given small doses of morphine. On Nov. 20, 1935, she was given her fifth treatment in the hypertherm. Examination before treatment revealed nothing new. The pulse rate was 90, the blood pressure 130 systolic and 70 diastolic and the rectal temperature 98.6 F.

11:00 a. m.: Patient placed in Kettering hypertherm

11:15 a. m.: Temperature, 101 F.; pulse rate, 110; patient noisy, restless and hyperactive; morphine, ⅙ grain (0.01 Gm.), subcutaneously

6. Histologic examination did not confirm the diagnosis of dementia paralytica. Neither perivascular infiltration nor neuronal atrophy was encountered.

12:00 m.: Temperature, 106 F.; pulse rate, 142; current turned off; patient left in cabinet covered with terry cloth towels

12:15 p. m.: Temperature, 106.6 F.; pulse rate, 150; in view of the rising temperature, patient was uncovered; intake of fluid, 800 cc.

12:25 p. m.: Temperature, 107.4 F.; pulse rate, 158; cyanosis of lips, ears and nail beds; fans directed on body; body sprayed with lukewarm water; fibrillation of heart

12:30 p. m.: Temperature, 107.4 F.; pulse rate, 153; fibrillation continued

12:36 p. m.: Blood pressure, 60 systolic and 30 diastolic; pulse rate, 150

12:46 p. m.: Temperature 107 F.; Pulse rate, 150; intravenous infusion of 0.9 per cent saline and 9 per cent dextrose solution started; cardiac irregularity continued

12:49 p. m.: Blood pressure, 60 systolic and 40 diastolic; pulse rate, 148; difficult to make out whether heart was fibrillating or whether there were extrasystoles; patient comatose; cyanosis of finger-tips

12:58 p. m.: Temperature, 106.4 F.; pulse rate, 156; blood pressure, 60 systolic and 40 diastolic; frequent extrasystoles at apex of heart

1:05 p. m.: Temperature 106.4 F.; pulse rate, 146; cyanosis of finger-tips persisted; inhalations of 5 per cent carbon dioxide and oxygen given by mask, with some relief of cyanosis; profuse discharge of yellowish white material from mouth

1:12 p. m.: Temperature, 104.6 F.; pulse rate, 140; blood pressure, 80 systolic and 60 diastolic; respiratory rate, 28; drooling of secretions from mouth continued

1:25 p. m.: Temperature, 104 F.; pulse rate, 126; blood pressure, 80 systolic and 40 diastolic

1:30 p. m.: 1,000 cc. of fluids already given intravenously; temperature, 104 F.; pulse rate, 132; respiratory rate, 28; coarse bubbling râles at base of both lungs; more pronounced on left

1:38 p. m.: Pulse rate, 128; blood pressure, 110 systolic and 30 diastolic; cyanosis of finger-tips persisted

1:47 p. m.: Temperature, 102 F.; pulse rate, 116; blood pressure, 130 systolic and 20 diastolic; respiratory rate, 28; patient still comatose

1:56 p. m.: Pulse rate, 114; blood pressure, 135 systolic and 30 diastolic; skin, cool; cyanosis of nail beds

2:00 p. m.: 1,500 cc. of fluids already given intravenously; temperature, 103 F.; pulse rate, 116; rigidity of lower extremities and left arm; flexion of fingers and toes on left; pupils, dilated, left greater than right; drooping of left lid and left side of mouth

2:14 p. m.: Temperature, 103 F.; repetition of seizure, with marked rigidity lasting eleven minutes; rigidity of left upper and lower extremities; weakness of right upper extremity and flexion of fingers and wrist

2:27 p. m.: Temperature, 103.8 F.; pulse rate, 120; blood pressure, 118 systolic and 60 diastolic; coma continued; skin, pale

2:45 p. m.: Temperature, 104 F.; pulse rate, 120; blood pressure, 86 systolic and 50 diastolic

3:00 p. m.: Temperature, 104 F.; pulse rate, 136; blood pressure, 85 systolic and 48 diastolic, inhalations of oxygen and 5 per cent carbon dioxide given for ten minutes, as breathing was labored, with occasional periods of apnea

3:02 p. m.: Intravenous infusion of 0.9 per cent saline and 10 per cent dextrose solution started

3:12 p. m.: Temperature, 104 F.: pulse rate, 136

3:15 p. m.: Pulse rate, 120; blood pressure, 88 systolic and 42 diastolic; patient, comatose; skin warm; good color except for slight cyanosis of nail beds

3:30 p. m.: Only 900 cc. of solution given intravenously, as breathing became labored; temperature, 103.6 F.; pulse rate, 134; inhalations of oxygen and 5 per cent carbon dioxide for ten minutes

3:40 p. m.: Pulse rate, 120; blood pressure, 112 systolic and 60 diastolic

3:50 p. m.: Pulse rate, 148; temperature, 103.6 F.; blood pressure, 150 systolic and 74 diastolic; respiratory rate, 20; Babinski reflex on left

4:05 p. m.: Temperature, 103.4 F.; pulse rate, 126; blood pressure, 106 systolic and 60 diastolic; epinephrine, 12 minims (0.74 cc.), subcutaneously

4:14 p. m.: Catheterization of bladder; 155 cc. of urine obtained; no sugar, diacetic acid or acetone

4:17 p. m.: Patient vomited 1 pint (475 cc.) of foul-smelling material

4:25 p. m.: Temperature, 102.6 F.; pulse rate, 112; blood pressure, 100 systolic and 60 diastolic; involuntary, foul dejecta

4:42 p. m.: Temperature, 102.6 F.; pulse rate, 111; blood pressure, 102 systolic and 58 diastolic

5:15 p. m.: Temperature, 102.8 F.; pulse rate, 108; blood pressure, 70 systolic and 50 diastolic

5:20 p. m.: Epinephrine, 8 minims (0.5 cc.), subcutaneously; pulse rate, 120; blood pressure, 70 systolic and 50 diastolic

5:26 p. m.: 50 cc. of 50 per cent solution of dextrose given intravenously, with 8 units of insulin subcutaneously; convulsive seizure occurred; turning of head to left and clonic and tonic movements of left upper extremity; Babinski sign on left

5:30 p. m.: Blood pressure, 82 systolic and 60 diastolic; patient, comatose; involuntary dejecta

6:00 p. m.: Recurrence of convulsive seizures; involuntary dejecta

6:17 p. m.: Cessation of convulsions; pulse rate, 96; blood pressure, 112 systolic and 80 diastolic; labored breathing; coughing

6:22 p. m.: Epinephrine, 8 minims (0.5 cc.); caffeine with sodium benzoate, 5 grains (0.3 Gm.), subcutaneously; repeated generalized convulsions; pulse rate, 120

6:30 p. m.: Temperature, 103.8 F.; pulse rate, 108; blood pressure, 110 systolic and 68 diastolic

6:45 p. m.: Temperature, 103.8 F.; pulse rate, 104; blood pressure, 80 systolic and 56 diastolic; respiratory rate, 24; patient, quiet; hands, cold and cyanotic

6:55 p. m.: Temperature, 104 F.; pulse rate, 108; blood pressure, 86 systolic and 60 diastolic; respiratory rate, 25; restlessness and groaning; mild generalized convulsion; head turned to the left; drooping of left side of mouth

7:05 p. m.: Temperature, 104.2 F.; pulse rate, 100; blood pressure, 82 systolic and 62 diastolic; hands, cold; nail beds, cyanosed; respirations, stertorous, with rate of 26

7:15 p. m.: Blood pressure, 80 systolic and 62 diastolic; epinephrine and caffeine repeated

7:30 p. m.: Blood pressure, 98 systolic and 60 diastolic; pulse rate, 104; temperature, 104.6 F.; hands, cold and cyanotic

7:45 p. m.: Pulse rate, 120; blood pressure, 96 systolic and 62 diastolic; respirations, deep, with rate of 20; atropine, 1/150 grain (0.4 mg.), for tracheal râles

7:50 p. m.: Temperature, 104.8 F.; pulse rate, 120; blood pressure, 78 systolic and 52 diastolic; respiratory rate, 40; sponging of body followed by convulsive seizures; groaning, resistance to handling, incontinence of urine and feces; vomiting of considerable amount of green watery material

7:57 p. m.: Temperature, 103.8 F.; pulse rate, 120 and irregular; tracheal râles; blood pressure, 84 systolic and 52 diastolic

8:10 p. m.: Pulse rate, 120; blood pressure, 68 systolic and 44 diastolic; vomiting of green, foul-smelling material; temperature, 104.6 F.; respiratory rate, 40 and labored; involuntary movements of bladder and bowel; twitchings of circumoral muscles; caffeine and epinephrine administered

8:20 p. m.: Pulse rate, 112; blood pressure, 52 systolic and 40 diastolic; respiratory rate, 40; complete ptosis of left upper lid

8:30 p. m.: Pulse rate, 130; blood pressure, 58 systolic and 40 diastolic

8:50 p. m.: Pulse rate, 112; blood pressure, 58 systolic and 40 diastolic; restlessness and groaning; many coarse râles scattered over both lungs

9:15 p. m.: Pulse rate, 120; blood pressure, 54 systolic and 40 diastolic; incontinence of urine and feces

9:20 p. m.: Caffeine and epinephrine subcutaneously; inhalations of oxygen and 5 per cent carbon dioxide

9:30 p. m.: Temperature, 105.4 F.; pulse rate, 140; respiratory rate, 46; blood pressure, 52 systolic and 40 diastolic; great restlessness

9:50 p. m.: Scopolamine hydrobromide, 1/100 grain (0.6 mg.), subcutaneously and paraldehyde, 2 cc., intramuscularly; inhalations of oxygen and 5 per cent carbon dioxide; mottled cyanosis of trunk

10:05 p. m.: Pulse rate, 118; temperature, 104.8 F.; blood pressure, 70 systolic and 50 diastolic; respiratory rate, 48; improved color of skin

10:25 p. m.: Temperature, 104.4 F.; pulse rate, 118; respiratory rate, 50; blood pressure, 72 systolic and 58 diastolic; mild convulsions

10:40 p. m.: Temperature, 104.2 F.; pulse rate, 110; blood pressure, 74 systolic and 52 diastolic; great restlessness; respiratory rate, 48; hands, cyanotic and cold; breathing, stertorous, with many tracheal râles

11:00 p. m.: Catheterization; normal urine; blood pressure, 70 systolic and 50 diastolic; pulse rate, 110 and irregular

11:25 p. m.: Temperature, 103.4 F.; pulse rate, 110 and irregular; blood pressure, 76 systolic

11:45 p. m.: Temperature, 103.8 F.; pulse rate, 110; blood pressure, 74 systolic and 56 diastolic; labored respirations, with rate of 48; pupils, round and equal; no reaction to light; reflexes of biceps and radialis muscles, active and equal; no triceps, patellar or ankle jerks; sugtive Babinski sign on right

12:00 m.: Temperature, 103 F.; pulse rate, 108; respiratory rate, 46; blood pressure, 70 systolic; pulse irregular; marked cyanosis; atropine, 1/100 grain (0.6 mg.), subcutaneously for pulmonary edema

12:20 a. m.: Temperature, 103 F.; pulse rate, 110; blood pressure, 80 systolic and 50 diastolic; cyanosis

12:45 a. m.: Temperature, 103 F.; pulse rate, 104 and irregular; blood pressure, 75 systolic

1:10 a. m.: Blood pressure, 70 systolic and 50 diastolic; cyanosis of nail beds marked; caffeine and epinephrine subcutaneously; inhalations of oxygen and 5 per cent carbon dioxide; poor condition

1:20 a. m.: Temperature, 104 F.; blood pressure, 70 systolic; caffeine, epinephrine and carbon dioxide and oxygen repeated.

1:35 a. m.: Pulse rate, 120; respiratory rate, 44; aspiration of trachea because of râles; blood-tinged fluid obtained

2:00 a. m.: Pulse rate, 144; temperature, 104 F.; increase of cyanosis; pulse of poor quality

2:10 a. m.: Pulse rate, 132; blood pressure, 60 systolic; respiration, shallow, with rate of 40; caffeine, epinephrine and carbon dioxide and oxygen repeated; respirations ceased

The outstanding observations in this case were vascular collapse with cardiac arrhythmia, coma, convulsions with neurologic changes, loss of sphincteric control and pulmonary edema. The blood pressure rose after stimulation, the intravenous administration of fluids and inhalations of 5 per cent carbon dioxide and oxygen, only to fall again rapidly. Permission for postmortem examination was granted.

The autopsy was performed by Dr. Anna Allen, and the histologic examination was made by Dr. Myrtelle M. Canavan, who gave us permission to publish a summary of the data.

Gross Postmortem Examination.—Both ankles were edematous. The fat over the thorax and abdomen was pale and edematous. There was continuous oozing of liquid blood from the cut surface of the abdomen and thorax. The muscles were somewhat pale. Many adhesions were noted between the omentum, the intestines and the anterior abdominal wall. The intestines were somewhat distended and deeply injected, and there was also a small amount of slightly blood-tinged fluid in the abdominal cavity. There were old adhesions at the apex of both lungs but no free fluid in the pleural cavities. The bronchial mucosa was somewhat injected, and the bronchi contained a small amount of frothy fluid.

Lungs: The left lung weighed 400 Gm. On section slight edema and slight diffuse congestion were noted and were more marked in the dependent portion. The right lung weighed 490 Gm. and showed more edema than did the left lung. In the lowest lobe there were scattered patchy hemorrhages.

Heart: The heart weighed 330 Gm. The epicardial fat was fairly abundant, pale and somewhat edematous. There was slight diffuse thickening of the epicardium. The free edge of the mitral valve was rolled over, thickened and wrinkled. Slight thickening at the base of the aortic cusps was present. The other valves were normal. The endocardium lining the left ventricle was slightly thickened, and a few subendocardial hemorrhages were present. The myocardium was somewhat pale but firm. There was an occasional patch of thickening in the aorta above the valve. The right coronary artery showed a few atheromatous plaques. The left coronary artery also showed some atheromatous changes.

Gastro-Intestinal Tract: The stomach mucosa was discolored and slightly swollen and that of the duodenum was injected. The mucosa of the jejunum was intensely swollen and hemorrhagic; it contained blood-stained liquid, as did the upper part of the ileum. At the ileocecal valve there were three hemorrhagic areas in the mucosa.

Liver: The liver weighed 1,830 Gm. and was soft and flabby. There were irregular patches of congestion and many light yellowish patches on the surface. The outlines of the lobules were blurred and swollen. Fatty changes were present throughout.

Kidneys: The right kidney weighed 170 Gm., and the left kidney 160 Gm. Both were normal except for the suggestion of cloudy swelling.

Adrenals: The right adrenal gland measured 4 by 4.5 by 1 cm. On section the center of the right adrenal gland was seen to be completely softened, with a large cavity. The cortex was thin and light yellow. The left adrenal gland measured 5.5 by 3 by 1 cm. The center of the medulla was firm and dark brown.

Brain: There was a small subdural hemorrhage, about 1 cm. in diameter, over the temporal region. The dura was adherent in the frontal region and thickened and tensely stretched over the brain. The dura over the right temporal region was more markedly thickened than elsewhere, and there was beginning membrane formation. Underneath the fairly recent hemorrhage the dura was stained yellow. The brain weighed 1,200 Gm. The pia mater over the vertex of the brain was moderately thickened, and there was intense injection of the pial blood vessels. Subdural blood, fairly recent (within twenty-four hours probably), was present in the middle fossa and over part of the tentorium cerebelli on the right side. There was a marked pressure cone, formed by the cerebellum around the medulla. The arteries at the base showed slight diffuse thickening, and in the basilar artery there was fusiform dilatation in the portion situated over the lower part of the pons. This aneurysmal dilatation extended for 1 cm. There was granular ependymitis in the floor of the fourth ventricle. The fourth ventricle was dilated.

The brain was fairly firm. On palpation, however, the pons appeared softer than the spinal cord. There was also a loss of consistency over the lateral ventricle, suggesting internal hydrocephalus.

Histologic Postmortem Examination.—The histologic examination, as resummarized by Dr. Canavan, revealed the followning information:

The heart was edematous and slightly fibrotic. The lungs showed edema, hyperemia, hemorrhages and exudations of various ages. The spleen presented some hyperemia of the vessels and moderate collections of lymph around the vessels. The liver showed cloudy swelling, periductal infiltration and hyperemia. The kidneys were hyperemic, and there was slight tubular degeneration. The adrenal glands showed slight degeneration of the cells, especially in the zona fasciculata. The stomach and small intestines were hyperemic and edematous. The brain showed chronic meningitis, subarachnoid hemorrhages, some thickening of the vessels in the subarachnoid space and subependymal gliosis in the basal ganglions.

COMMENT

An examination of the observations made shows that in hyperpyrexia induced by hot moist air there are disturbances in four mechanisms of the Blalock classification [1a] by means of which shock, or acute failure of the circulation, may occur:

1. Hematogenic—due to the reduction of the volume of blood
2. Vasogenic—due to the effect of heat per se on the capillaries
3. Neurogenic—due to stimuli acting through the nervous system
4. Cardiogenic—a probable but not an important factor

Hyperpyrexia induced by hot moist air causes (chart 1):

I. A diminished total blood volume which leads to
  A. A slowing of the blood flow and a diminished venous return, causing a lessened cardiac output and resulting in
    a. Relative anoxemia, which in turn leads to
      1. Increased capillary permeability with
      2. Further reduction in the blood volume

II. A probable direct effect on the capillary endothelium, resulting in increased capillary permeability

III. An increase in the metabolic rate requiring an increased supply of blood and oxygen, i. e., a greater demand under adverse conditions, and tending to cause
  A. A further rise in the body temperature

IV. Interference with the absorption of fluids from the gastro-intestinal tract, making it difficult to offset the loss of fluids from sweating

V. A probable increase in the output of epinephrine, resulting in
  A. Constriction of the precapillary vessels already constricted and leading to
    a. Further reduction in blood flow
      1. Greater anoxemia
      2. Increased capillary permeability

VI. A possible effect on the nervous system
  A. Through changes in the brain cells as a result of hyperpyrexia per se, partial anoxemia and disturbance in the p_H of the blood
  B. A lessened and disturbed control by the central temperature mechanism
  C. Increased intracranial pressure as a result of cerebral edema
  D. Disturbances in respiration due to
    a. Alkalosis
    b. Increased intracranial pressure
    c. Anoxemia

Blood Volume.—Investigations [7] of patients in this clinic during hyperpyrexia induced by hot moist air under conditions similar to those for the group of patients reported on here have revealed by the dye method of Gregersen and his co-workers [8] that there is invariably a

7. This work was completed in our clinic in conjunction with Drs. J. G. Gibson 2d and W. A. Evans Jr. and is now ready for publication.

8. Gregersen, M. I.; Gibson, J. J., and Stead, E. A.: Plasma Volume Determination With Dyes, Am. J. Physiol. **113**:54 (Sept.) 1935.

reduction in the volume of blood plasma, ranging from 10 to 32 per cent, accompanied with increases in the hematocrit values of from 3 to 9 per cent.

In one patient (J. P. of the group under discussion) who was exposed to the hypertherm over a period of two and three quarter hours and in whom the temperature level fluctuated for an additional two and

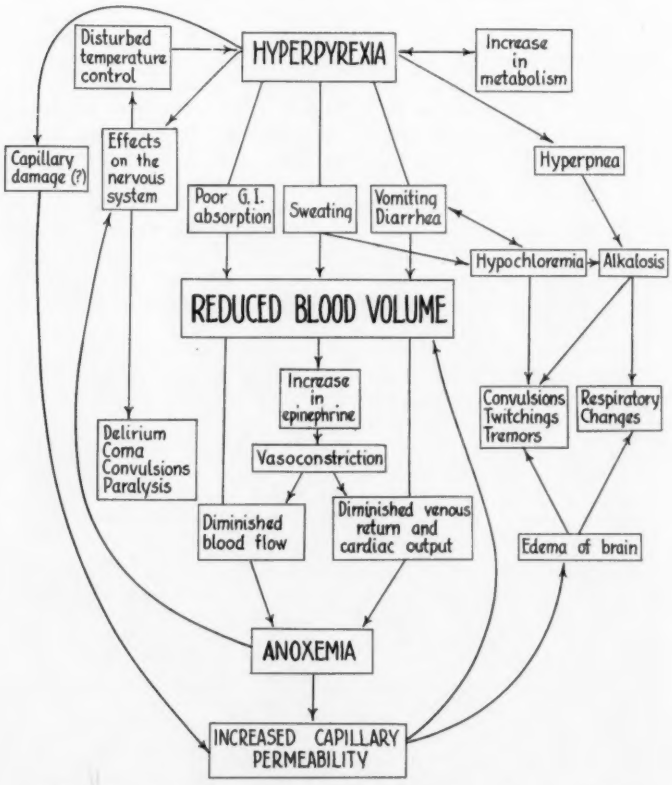

Chart 1.—The mechanism of shock in therapeutic hyperpyrexia.

one quarter hours between 105 and 106 F., the volume of blood plasma was reduced as much as 32 per cent, even though the intake of fluid during the entire period was 3,000 cc. of 0.4 per cent saline solution. The loss in body weight, representing fluids lost as a result of treatment, was 1¼ pounds (0.6 Kg.). This patient did not go into shock. In a second patient (H. H.) shock resulted on two occasions when the plasma volume was reduced 21 and 27 per cent at temperature levels of 106.4

and 105.6 F., respectively, after exposures of two and three hours. The intake of fluid was less than 500 cc. of saline solution on each occasion, and the loss in body weight was 6½ and 7½ pounds (3 and 3.5 Kg.), respectively. In a third patient (J. S.) the body temperature was raised to 105 F. in one and five-sixth hours and was prolonged for nearly two hours at a level ranging from 105 to 106.1 F. An intake of 750 cc. per hour of 0.6 per cent saline solution was recorded during the rise, prolongation and fall in the body temperature, making a total intake of 4,000 cc. Despite a gain of 4¼ pounds (2 Kg.) in the body weight, the plasma volume showed a maximum concentration of 12.5 per cent.

Further confirmation of the finding of a reduced volume of blood by the method used is afforded by the following observations:

One of the patients (H. H.) in whom shock occurred at a temperature of 106.4 F., with a diminution in the plasma volume of 21 per cent, had an increase in the plasma volume to about the original level (6 per cent concentration) after an intravenous infusion of 1,350 cc. of 0.9 per cent saline and 10 per cent dextrose solution (chart 2). The hematocrit value, which had increased from a basal level of from 45 to 51.5 per cent at the height of blood concentration, fluctuated from 45.5 to 47 per cent during and after the intravenous infusion.

One deduces the importance of the blood volume from the observations of Hartman and Major [9] in experiments on dogs. The animals were given morphine or sodium amytal, and the body temperature was raised and maintained at levels from 108 to 109 F. for from seven to nine hours by means of the Kettering hypertherm. Two bouts of fever were given in thirty-six hours. Only the animals which received repeated intravenous infusions of dextrose or mixtures of dextrose and saline solution survived. On the other hand, despite the ingestion of an amount of saline solution by mouth equivalent to the amount of salt and water lost during the procedure, the animals not receiving intravenous infusions died as a result of vascular collapse.

Because of the concentration of blood there occurs slowing of circulation, an insufficient venous return and a diminished cardiac output. The blood supply of the capillaries is interfered with, and capillary dilatation becomes more marked, because of a lack of oxygen, a diminished supply of the "tonic hormone" secreted by the pituitary gland [10] or an insufficient blood supply to the vasomotor center in the brain.[11]

9. Hartman, F. W., and Major, R. C.: Pathological Changes Resulting from Accurately Controlled Artificial Fever, Abstr. of Papers, Ann. Fever Conf., 1935, p. 67; Am. J. Clin. Path. **5**:392 (Sept.) 1935.

10. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1924, p. 258.

11. Harrison,[1d] p. 19.

The reduction in the blood volume is evidently not the only important factor concerned in our series. Marked concentration of the blood plasma, which, at a temperature of 106 F. or above was accompanied with shock, has been found in the same patient at lower body tempera-

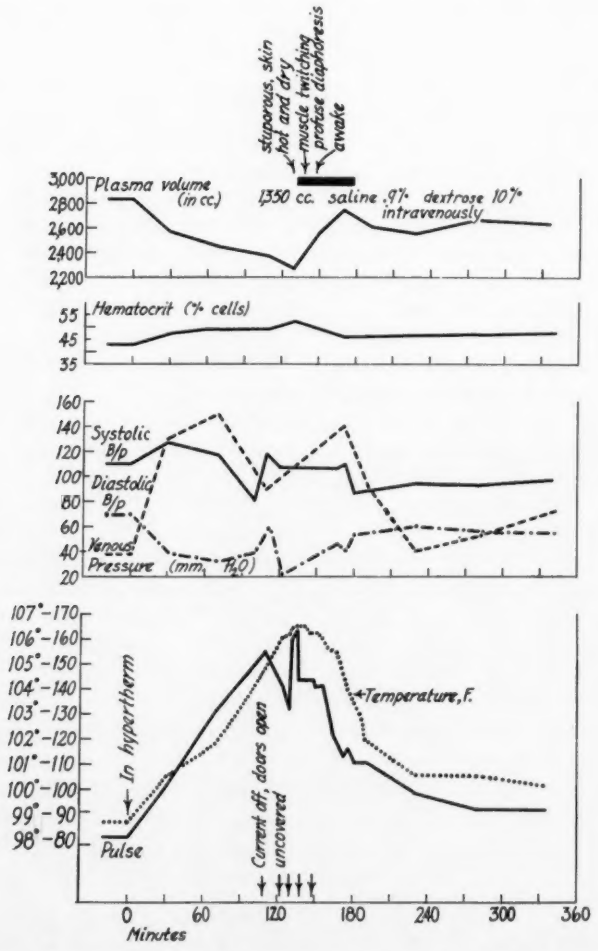

Chart 2.—The concomitants of shock occurring in hypertherm hyperpyrexia: plasma volume, hematocrit readings; arterial and venous blood pressures, pulse rate and body temperature, showing the changes induced by intravenous infusion and cooling the body.

tures without shock.[7] Talbott [4] has found marked concentration of the blood in patients exposed to high dry temperatures in whom heat cramps occurred, while few other constitutional symptoms were present. Only slight rises in the body temperature of these patients occurred.

The permeability of the lymphatic capillaries has been found to be increased when the temperature of the part is raised.[12] The edema of the hands seen occasionally after hypertherm hyperpyrexia is indicative of altered capillary permeability. Krogh has stated that normally the permeability of the capillaries is increased by dilatation and, as a general rule, those physical and chemical agents which give rise to capillary dilation will also, when applied in sufficient strength, cause edema or stasis or both.[13] Artificial fever, induced by high external temperatures with the prevention of loss of heat, is an ideal dilator of the capillaries and must be included in the group of physical agents specified by Krogh. The increase in capillary permeability due to the effect of heat per se and anoxemia causes a still further reduction in the blood volume, and a vicious circle is thus produced.[14] The microscopic examination of the tissues in our fatal case revealed vasodilatation and increased capillary permeability, as shown by the edema of the heart; edema, hyperemia, hemorrhages and exudates of the lungs; hyperemia of the liver and kidneys; hyperemia and edema of the gastro-intestinal tract, and edema, hemorrhages and hyperemia of the brain and its membranes.

Metabolic Rate.—An increase in the metabolic rate of from 5 to 14 per cent for each degree of rise in temperature has been found in therapeutic hyperpyrexia.[18] It has also been observed that the increment of rise in the metabolic rate per degree of fever tends to increase

12. Hudack, S. S., and McMaster, P. D., cited by Bierman, W.: Radiothermy: Fever Induced by Short Radio Waves, Arch. Phys. Therapy **13**:389 (July) 1932.

13. Krogh,[10] pp. 232 and 235.

14. The use of sedatives of the morphine and barbituric acid series during hypertherm hyperpyrexia is dangerous. The combined capillary dilator effects of fever and of the anesthetic may result in marked loss of tone, with greater liability of shock.[15] The rise in temperature is more rapid,[16] the control of the temperature is more difficult and the water shifting mechanism is disturbed.[17] Sodium amytal may produce capillary damage.[9]

15. Krogh,[10] p. 125.

16. Sheard, C.: Thermal Changes Produced in Various Tissues of Animals by Systemic and Local Applications of Radiothermy, Abstr. of Papers, Ann. Fever Conf., 1935, p. 42.

17. Barbour, H. G.: Heat Regulation and Water Exchange: The Effects of Hot and Cold Baths upon Blood Concentration and Brain Volume in Dogs, Am. J. Physiol. **67**:366, 1924.

18. Kopp, I.: Metabolic Rates in Therapeutic Fever, Am. J. M. Sc. **190**:491 (Oct.) 1935.

sharply at levels of 106 F. and above.[19] It is obvious therefore that the demands on the organism are greater at these levels of temperature at a time when the volume of blood is considerably reduced, the circulatory rate diminished and oxygenation interfered with. The increased metabolism creates more heat in the body, while the dissipation of heat by evaporation of sweat from the surface of the skin is greatly impeded by dehydration and by the high dry and wet bulb temperatures surrounding the body.

Impaired Absorption of Fluids.—Absorption of fluid from the gastro-intestinal tract during hypertherm hyperpyrexia is either delayed or impaired, as revealed by our own experiments and by the work of Hartman and Major.[9] It is further confirmed by the following observations:

1. The blood volume remains below normal, despite the taking of large quantities of fluid by mouth, even though there is an increase in body weight during treatment.

2. The blood volume can be maintained at a normal level only by continuous intravenous infusion of large amounts of fluid.[7]

3. The amount of fluid vomited during therapy in many instances is as great as the total intake of fluid over a period of one or two hours.

Increased Output of Epinephrine.—An increase in the output of epinephrine is suggested by marked rises in systolic blood pressure and pulse rate both during the ordinary course of fever and just prior to shock. For example, in the patient (H. H.) in whom shock occurred at a temperature of 106.4 F., with a plasma concentration of 21 per cent, a rapid increase in the pulse rate from 132 to 164 and a rise in systolic blood pressure from 80 to 118 mm. were noted before the reaction occurred (chart 2). Marked rises in the systolic blood pressure as high as 300 mm. and in the pulse rate to 180 per minute have been noted in other patients at temperature levels of 106 F. or higher during the ordinary course of fever treatment. Experimental evidence has been offered by Freeman and his co-workers [20] that dehydration increases the output of epinephrine. He reasoned that partial asphyxia results from the diminution in blood volume, increase in blood viscosity and diminution in blood flow due to dehydration and that these factors are responsible for an increase in the output of epinephrine. Microscopic examination of the adrenal glands of our patient and of others reported on in the literature as having died as a result of hypertherm hyperpyrexia

19. Kopp, I.: Unpublished data.

20. Freeman, N. E.; Morison, R. S., and Sawyer, M. E. M.: Effect of Dehydration on Adrenal Secretion and Its Relation to Shock, Am. J. Physiol. **104**:628 (June) 1933.

revealed degeneration of cells, especially in the zona fasciculata. Cramer [21] has pointed out that the postmortem pictures of heat stroke were typical of hyperaction followed by exhaustion of the thyroid and the adrenal glands.

The increased output of epinephrine during shock due to hyperpyrexia exaggerates the state of shock by reducing still further a diminished blood volume.[22] Vasoconstriction results—a condition which is already present during these reactions and which, if beyond an optimal degree, aggravates the circulatory failure by interfering with the venous return to the heart, which is already inadequate, and thus the cardiac output is still further reduced.[23] The anoxemia thereupon is more marked, and the capillary permeability is increased.

The Presence of a Neurogenic Factor.—It seems almost obvious that the nervous mechanism plays a distinct rôle in shock due to hypertherm fever, but in the present state of knowledge it is not possible to evaluate its rôle correctly. It is probable that both the autonomic and the cerebral nervous system are implicated.

It is generally recognized that stimulation of the sympathetic system is capable of producing shock. For example, shock occasionally occurs after a bullet wound, a blow in the solar plexus or coronary thrombosis, which lead to extreme vasodilatation.[24] It has already been stated that hypertherm hyperpyrexia, by causing dehydration, stimulates the sympathico-adrenal system.[20] It is also recognized that changes in environmental temperature and humidity cause activity of the sympathetic system in an attempt to meet the exigencies of the situation.[25] When the demand on this system is too great or too sudden, a breakdown occurs. In our experience there is a distinct relationship between the wet bulb temperature and bad reactions. Certainly, the patient's discomfort is definitely related to this factor. Vomiting occurs much more frequently when the wet bulb level is high than when it is low. Shock phenomenon in our patients occurred only when they were in the hypertherm, where the wet bulb temperature approximates 135 F., and never in the diathermy-carbon lamp machine, where it is about 105 F. This is in consonance with the well known fact that a high external temperature with a low humidity is well tolerated.[26] Haldane has clearly demonstrated that severe reactions depend on the height of

21. Cramer, W., cited by Hill.[5]

22. Gibson, J. G.: Personal communication to the authors. Erlanger, J., and Gasser, H. S., cited by Moon.[1b]

23. Eggleston, C.: The Pharmacopeia and the Physician: Drugs Used in the Treatment of Circulatory Failure in Acute Infectious Diseases, J. A. M. A. **107:** 1213 (Oct. 10) 1936.

24. Blalock.[1a] Harrison.[1d] Atchley.[2a]

25. McConnell, W. J.: Correlation of Skin Temperatures and Physiological Reactions, Am. J. Soc. Heat. & Vent. Engin. **30:**457, 1924.

26. Haldane, J. S.: Influence of High Air Temperatures, J. Hyg. **5:**494, 1905.

the absolute wet bulb level.[26] Likewise Hall and Wakefield[27] showed that the time necessary to produce heat stroke in dogs subjected to high humid temperatures was generally proportional to the height of wet bulb temperatures.

The cerebral nerve cells are rather more readily damaged by high temperature than are less specialized cells of the body. The cerebral ganglion cells of experimental animals which died as a result of hypertherm hyperpyrexia at temperatures ranging from 108 to 109 F. showed shrinkage and pyknosis.[9] The temperature levels reached in some patients are not far below these levels and are near enough to suggest an interference in function if not in structure. In addition to the temperature itself, the cerebral cells are exposed to relative anoxemia due to a diminution in blood volume. Alkalosis is still another noxious state. Evidence of disturbed function of the cerebral mechanism is frequently encountered in the treatments in the form of projectile vomiting and delirium. In the shock reactions there are, in addition, coma, muscle tremors, muscle twitchings and convulsions.

The symptoms of tetany that are occasionally seen are characterized by muscle rigidity, tonic and clonic convulsive seizures of the extremities and abdomen and fibrillary twitchings. Alkalosis occurs in hypertherm hyperpyrexia[28] and is dependent on: (*a*) a loss of carbon dioxide by hyperventilation and (*b*) a loss of chloride, due to excessive sweating. Although sodium also is lost, this is not so important as the loss of carbon dioxide and chloride. There is also some loss of chloride as a result of vomiting and diarrhea. Some of the loss of sodium chloride is made up by the ingestion of saline solution by mouth, provided absorption takes place.

Pathologic Observations.—The pathologic observations made in our fatal case agreed essentially with those reported for two patients by Hartman and Major,[9] with the exception that in their patients hemorrhagic encephalitis was present. The other essential features are:

1. Edema of the lungs, intestines and liver
2. Hyperemia of the intestines, liver, kidneys and spleen, congestion of the lungs and intense injection of the pial vessels
3. Subdural and subendocardial hemorrhages and hemorrhages of the lungs and intestines
4. Degeneration of the liver, tubular degeneration of the kidneys and vacuolar degeneration of the adrenal glands
5. A pressure cone around the medulla.

27. Hall, W. W., and Wakefield, E. G.: Study of Experimental Heat-Stroke, J. A. M. A. **89**:177 (July 16) 1927.

28. Work completed in this clinic in conjunction with Drs. M. Pijoan and J. G. Gibson 2d and now ready for publication.

These observations are similar to those for dogs in which fever was induced by means of the Kettering hypertherm,[9] to those reported as typical of heat stroke,[29] and to those of the shock syndrome occurring under other conditions.[1b] The edema, congestion and hemorrhages are due to the physiologic disturbances already described as occurring in hypertherm hyperpyrexia. The degeneration of tissue is probably due in great part to the height of fever and in a lesser degree to relative anoxemia and a change in the p_H of the blood.

Treatment.—On the basis of the foregoing discussion, the treatment of shock due to hyperpyrexia must attempt to: (1) reduce the body temperature, (2) overcome the dehydration and (3) remedy the alkalosis and hypochloremia. The following procedure is therefore carried out:

1. The patient is immediately removed from the fever cabinet and uncovered. The body surface is sprayed with lukewarm water, and evaporation is hastened by electric fans to reduce the body temperature rapidly. (The application of ice or cold water causes constriction of the surface capillaries and interferes with the loss of heat. Hill [5] has stated that the evaporation of water at body temperature carries away 0.59 calories of heat per gram, while the melting of ice removes only 0.08 calories of heat per gram.)

2. Intravenous infusions of isotonic saline and 5 per cent dextrose solution in amounts ranging from 850 to 1,500 cc. are given. Large amounts of fluid are necessary to raise the plasma volume to normal levels, but the dangers of overburdening the circulation with the production of pulmonary edema should be kept in mind, since this has been an important feature in fatal cases. Repeated determinations of the venous pressure should prevent this danger, but if pulmonary edema is present, small amounts of hypertonic solution are indicated.

The use of small amounts of hypertonic saline or dextrose solution to increase the blood volume to normal is of little value, since the body tissues are dehydrated and little fluid reserve is present that can be safely drawn on. It is true, however, that when hyperpyrexia is present, the patient is in collapse and the skin is hot and dry, the intravenous infusion of 100 cc. of 50 per cent solution of dextrose is followed by some rise in the plasma volume, profuse diaphoresis and a fall in the body temperature.[7] The patient, however, remains in a critical condition; the blood pressure is low, the pulse is rapid and the plasma volume falls again. Hypertonic solutions may have some value through their ability to reduce cerebral edema. The protracted use of hypertonic dextrose solution intravenously, however, is inadequate, since it tends to increase the intensity of shock by dehydration.[2a]

29. Gauss, H., and Meyer, K. A.: Heat Stroke: Report of One Hundred and Fifty-Eight Cases from Cook County Hospital, Chicago, Am. J. M. Sc. **154**:554 (Oct.) 1917. Hill.[5]

3. Inhalations of oxygen and 5 per cent carbon dioxide are given. This is an ideal respiratory stimulant; it supplies the body with carbon dioxide to compensate for the alkalosis, it reduces the cyanosis when present and it lessens the capillary permeability by relieving the anoxemia.

4. Paraldehyde by rectum and soluble phenobarbital U. S. P. (sodium phenobarbital) intramuscularly are administered if the patient is extremely restless or if repeated convulsions occur.

5. When circulatory stimulants are indicated and when the aforementioned measures have not been successful, caffeine with sodium benzoate, 7½ grains (0.5 Gm.), is given subcutaneously every two hours. The use of epinephrine is now avoided for the reasons previously mentioned. Strychnine in large doses, 1/20 to 1/15 grain (3 to 4 mg.), every two or three hours subcutaneously is advised by some,[30] since it tends to increase the blood volume, stimulate the oxidative processes and decrease the capillary permeability. Pitressin, 0.5 to 1 cc. subcutaneously every three hours, is also commended, because of its ability to reduce capillary permeability.[30]

SUMMARY

Evidence is presented that severe reactions and death as a result of hyperpyrexia induced by exposure to hot moist air with the prevention of loss of heat are due to the shock syndrome.

The mechanism of shock under these conditions consists of a diminution in the blood volume, an increase in the vascular bed and an increase in the vascular permeability.

A disturbed neurogenic mechanism, in addition to a disturbed hematogenic mechanism (dehydration), is also present.

The presence of alkalosis and hypochloremia during artificial hyperpyrexia modify the clinical picture of the shock syndrome.

The pathologic picture is similar to that observed in shock in other conditions and in heat stroke. Of especial importance is the presence of degenerative changes in the adrenal cortex.

A plan of treatment is offered in an attempt to reduce the body temperature, to increase the volume of blood, to diminish the capillary permeability and to compensate for the alkalosis and the loss of chlorides by (1) the evaporation of lukewarm water from the body surface, (2) intravenous infusions and (3) inhalations of carbon dioxide and oxygen.

30. Warfield, L. M.: The Treatment of Circulatory Failure, J. A. M. A. **106**: 892 (March 14) 1936.

IMMUNOLOGIC STUDIES OF SICKLE CELL ANEMIA

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With the exception of the work reported by Diggs [1] and that of Beck and Hertz,[2] practically none of the articles on sickle cell anemia published in the past five years includes investigative work on the subject. It seems that knowledge of the disease has reached an impasse at present and that all writing henceforth must consist of case reports and summarizations of the literature until a new stimulus arises to give further impetus to the study of the condition and an understanding of the facts at hand. The present information on this disease has done no more than give possible leads to the cause of the sickling phenomena. No one has yet found the cause, and, most important from the standpoint of the patient, no one has found an effective therapeutic regimen or agent that will materially help the patient in the active anemic stage of the disease. The challenge to medicine, therefore, still exists, and, as will be shown, the prevalence of cases of potential anemia is somewhat startling.

No attempt is made to summarize completely all the literature on sickle cell anemia since its description by Herrick [3] twenty-six years ago. Articles with excellent summaries have been written by Steinberg [4] and by Anderson and Ware.[5] For purposes of brevity here the pertinent facts that have been established appear to be adequate. Hahn and Gillespie [6] have briefly listed the data from previous experimentations

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1. Diggs, L. W.: Negative Results in the Treatment of Sickle Cell Anemia, Am. J. M. Sc. **187**:521 (April) 1934.

2. Beck, J. P., and Hertz, C. S.: Standardizing Sickle Cell Method and Evidence of Sickle Cell Trait, Am. J. Clin. Path. **5**:325 (July) 1935.

3. Herrick, J. B.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Arch. Int. Med. **6**:517 (Nov.) 1910.

4. Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876 (April) 1930.

5. Anderson, W. W., and Ware, R. L.: Sickle Cell Anemia, Am. J. Dis. Child. **44**:1055 (Nov.) 1932; J. A. M. A. **99**:902 (Sept. 10) 1932.

6. Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia, Arch. Int. Med. **39**:233 (Feb.) 1927.

on the condition up to 1927. Their summary is reproduced here together with the results of their own experiments and those of subsequent investigators.

1. Sickle cell formation is retarded by cold and accelerated by heat (Sydenstricker [7]).
2. Sickle cell formation is independent of exposure to light, although return to spherical shape is more rapid in the dark (Huck [8]).
3. Serum is not essential to sickle cell formation, as the susceptible cells undergo the distortion when suspended in saline solution or citrated saline solution (Huck [8] and Hahn and Gillespie,[6] refuted by Sydenstricker [7]).
4. Susceptible cells, washed, become sickle cells in normal serum of persons of the same blood type (Sydenstricker [7] and Huck [8]).
5. Normal cells do not become sickle cells by the action of serum of a person whose blood contains sickle cells (Sydenstricker [7] and Huck [8]).
6. Bile pigment and bile salts accelerate sickle cell formation (Sydenstricker [7]).
7. Phagocytosis of sickle cells by large mononuclear cells occurs in vitro (Sydenstricker [7] and Emmel [9]).
8. Large mononuclear cells of a person whose blood contains sickle cells do not phagocytose normal blood cells (Sydenstricker [7] and Emmel [9]).
9. The production of sickle cells is inconstant in preparations made under identical conditions (Graham [10]).
10. Sickle cells are observed in tissues of affected subjects taken post mortem when the tissues are fixed in solution of formaldehyde. When Zenker's solution is used, sickle cells are not present (Graham and McCarty [11]).

After listing the foregoing data from previous investigations, Hahn and Gillespie reported their own investigations, which are now listed to continue the sequence of major facts available on sickle cell anemia:

11. Sickle cell formation is induced when a suspension of susceptible cells in saline or citrated saline solution is placed in an atmosphere of carbon dioxide, nitrous oxide or hydrogen. They will revert to the discoid form when the atmosphere is changed to diatomic oxygen or carbon monoxide.
12. Acidification of a suspension of susceptible cells up to the point of beginning hemolysis favors the sickle cell reaction.
13. A suspension of sickle cells buffered to a p_H of 6.8 in an atmosphere of ethylene will cause immediate sickling in five minutes, whereas in neutral solution this gas did not produce sickling.

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7. Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia, Am. J. Dis. Child. **26**:132 (Aug.) 1923.

8. Huck, J. G.: Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **34**:335 (Oct.) 1923.

9. Emmel, V. E.: A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**:586, (Oct.) 1917.

10. Graham, G. S.: A Case of Sickle Cell Anemia with Necropsy, Arch. Int. Med. **34**:778 (Dec.) 1924.

11. Graham, G. S., and McCarty, S. H.: Notes on Sickle Cell Anemia, J. Lab. & Clin. Med. **12**:536 (March) 1927.

During the same year that this work was done Josephs [12] reported his experiments on sickle cell anemia. The sequence is continued with his statement:

> 14. Some plasma component exists in all specimens of blood which cause sickling, but only the cells of patients who show the sickling phenomena are susceptible to it.

Josephs is credited by some authors with having made a discovery which Huck overlooked. His work, in any case, refuted that of Huck and of Hahn and Gillespie and supported that of Sydenstricker (see number 3 of the foregoing listed data). Hahn,[13] however, later reported work which he claimed in turn refuted that of Josephs.

Little experimental investigation was reported on this disease between 1927 and 1932. Miyamoto and Korb [14] reported the incidence of the sickling phenomena in 400 persons in St. Louis. To this may be added the series of patients tested by Cooley and Lee, Graham and McCarty and others, as will be subsequently shown. Complete reports of pathologic observations were made by Jaffé,[15] Sydenstricker,[16] Yater and Mollari [17] and others. Most interesting was the report of a case by Cooley and Lee,[18] which definitely refuted the statements of previous authors that sickle cells occur only in Negroes. They described an authentic case in a Greek child. Previous similar reports had been made (Castana,[19] Archibald [20] and Stewart [21]), but each case was questioned as to its authenticity because of the possibility (which the authors did not rule out) of admixture of Negro blood. Subsequent to Cooley's article, many reports had been made of proved cases among non-Negroes,

12. Josephs, H. W.: Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **40**:77 (Feb.) 1927.

13. Hahn, E. V.: Sickle-Cell (Drepanocytic) Anemia, Am. J. M. Sc. **175**: 206 (Feb.) 1928.

14. Miyamoto, K., and Korb, J. H.: Meniscocytes (Latent Sickle Cell Anemia): Its Incidence in St. Louis, South. M. J. **20**:912 (Dec.) 1927.

15. Jaffé, R.: Die Sichelzellenanämie, Virchows Arch. f. path. Anat. **265**:452, 1927.

16. Sydenstricker, V. P.: Sickle Cell Anemia, M. Clin. North America **12**:1451 (March) 1929.

17. Yater, W. M., and Mollari, M.: The Pathology of Sickle-Cell Anemia: Report of a Case with Death During an "Abdominal Crisis," J. A. M. A. **96**: 1671 (May 16) 1931.

18. Cooley, T. B., and Lee, P.: Sickle Cell Anemia in a Greek Family, Am. J. Dis. Child. **38**:103 (July) 1929.

19. Castana, V.: Gigantocytes and Sickle Cells, Pediatria **33**:431 (April 15) 1925.

20. Archibald, R. G.: Sickle Cell Anemia in the Sudan, Tr. Roy. Soc. Trop. Med. & Hyg. **19**:389 (Jan.) 1926.

21. Stewart, W. B.: Sickle Cell Anemia: Report of Case with Splenectomy, Am. J. Dis. Child. **34**:72 (July) 1927.

for instance those by Sights and Simon,[22] Rosenfeld and Pincus,[23] Cooke and Mack,[24] Pollock and Dameshek [25] and Wallace and Killingsworth.[26] Several cases in which splenectomy was used in treatment of the disease were reported by Bell [27] (including that of a patient operated on by Cooley and Lee), Hahn [13] and Ching and Diggs. [28] Penberthy and Cooley [29] reported in 1935 the results in 4 cases in which splenectomy was performed. One patient had been observed by them for six years. An interesting occasional finding of clinical interest is given in the reports submitted of osseous changes in the disease by Moore,[30] Vogt and Diamond,[31] Brandau,[32] de Castro [33] and Grinnan.[34] Recently Campbell [35] reported 6 cases in each of which there were acute abdominal manifestations, a symptom of which previous authors had made mention. Four of these patients were operated on; the findings were normal in 3 cases, and the fourth patient had cholecystitis and cholelithiasis. This fourth patient had a normal postoperative convalescence. The 2 patients who were not operated on had no symptoms a few days after admission to the hospital.

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22. Sights, W. P., and Simon, S. D.: Marked Erythrocytic Sickling in White Adults, Associated with Anemia, Syphilis and Malaria, J. Med. **12**:177 (June) 1931.

23. Rosenfeld, S., and Pincus, J. B.: The Occurrence of Sicklemia in the White Race, Am. J. M. Sc. **184**:674 (Nov.) 1932.

24. Cooke, J. V., and Mack, J. K.: Sickle-Cell Anemia in a White American Family, J. Pediat. **5**:601 (Nov.) 1934.

25. Pollock, L. H., and Dameshek, W.: Elongation of Red Blood Cell in a Jewish Family, Am. J. M. Sc. **188**:822 (Dec.) 1934.

26. Wallace, S. A., and Killingsworth, W. P.: Sicklemia in the Mexican Race, Am. J. Dis. Child. **50**:1208 (Nov.) 1935.

27. Bell, A. J.; Mitchell, A. J.; Cooley, T. B., and Lee, P.: Sickle Cell Anemia: Report of Two Cases in Young Children in Which Splenectomy Was Performed, Am. J. Dis. Child. **34**:923 (Dec.) 1927.

28. Ching, R. E., and Diggs, L. W.: Splenectomy in Sickle Cell Anemia, Arch. Int. Med. **51**:100 (Jan.) 1933.

29. Penberthy, G. C., and Cooley, T. B.: Results of Splenectomy in Childhood, Ann. Surg. **102**:645 (Oct.) 1935.

30. Moore, S.: Bone Changes in Sickle Cell Anemia with Note on Similar Changes Observed in Skulls of Ancient Mayan Indians, J. Missouri M. A. **26**: 561 (Nov.) 1929.

31. Vogt, E. C., and Diamond, L. K.: Congenital Anemias Roentgenologically Considered, Am. J. Roentgenol. **23**:625 (June) 1930.

32. Brandau, G. M.: Sickle Cell Anemia: Report of a Case, Arch. Int. Med. **50**:635 (Oct.) 1932.

33. de Castro, A. S.: Sickle Cell Anemia, J. de pediat., Rio de Janeiro **1**:427 (Nov.) 1934.

34. Grinnan, A. G.: Roentgenologic Bone Changes in Sickle Cell and Erythroblastic Anemia, Am. J. Roentgenol. **34**:297 (Sept.) 1935.

35. Campbell, E. H., Jr.: Acute Abdominal Pain in Sickle Cell Anemia, Arch. Surg. **31**:607 (Oct.) 1935.

Diggs [36] presented the first investigative report published since 1927, in which he attempted to show that the "rate of sickling is not related necessarily to the immediate severity of the anemia but to the chronicity of the anemia." He [1] was the first author to report an attempt at a therapeutic regimen with anywhere near an adequate number of patients, in that he described unsuccessful results of the treatment of 7 actively anemic patients using various antianemic agents. In one other instance [37] the successful treatment of a patient with an acute abdominal crisis was reported, and other authors had previously reported the treatment of single patients with results contrary to those of Diggs.

Perhaps the best contribution to the future investigative study of sickle cell anemia is the "standardizing sickle cell method" recently reported by Beck and Hertz.[2] The method consists of fixing the red blood cells with solution of formaldehyde after they have been allowed to assume their characteristic sickle form in a test tube containing equal parts of physiologic solution of sodium chloride and 3 per cent solution of sodium citrate overlaid with liquid petrolatum. The test is based on the observations previously reported by Hahn [13] that solution of formaldehyde will fix the cells in the sickling deformity. By this method, for a small series of patients these workers obtained a higher percentage of positive results (13 per cent) than has ever been reported. They admitted, however, that this result must be verified by a larger series of tests.

STATEMENT OF PROBLEM

After a survey of the literature it was found that with the exception of the few studies of blood grouping made on a small number of patients by Huck [8] and later by Huck and Guthrie,[38] no one had made a study of the immunologic aspects of sickle cell anemia. There are a number of facts that have led to the suggestion that an investigation of the immunologic properties of red blood cells having the sickling trait might be profitable. The sickle cell phenomenon and the isohemo-agglutinating characteristics are each peculiar to red blood cells. It has been definitely shown that each characteristic is inheritable. That the inheritance of isohemo-agglutination has a definite racial distribution has been shown by Snyder,[39] who quoted the discovery by L. Hirszfeld

36. Diggs, L. W.: The Sickle Cell Phenomenon: Rate of Sickling in Moist Preparations, J. Lab. & Clin. Med. **17**:913 (June) 1932.

37. Torrance, E. G., and Schnabel, T. G.: Potassium Sulphocyanate: A Note on Its Use for the Painful Crisis in Sickle Cell Anemia, Ann. Int. Med. **6**:782 (Dec.) 1932.

38. Huck, J. G., and Guthrie, C. G.: On the Existence of More Than Four Iso-Agglutinin Groups in Human Blood, Bull. Johns Hopkins Hosp. **34**:37 (Feb.) 1923.

39. Snyder, L. H.: Blood Grouping in Relation to Clinical and Legal Medicine, Baltimore, Williams & Wilkins Company, 1929.

and H. Hirszfeld. He demonstrated that the blood type follows a definite racial index or frequency. It is not unreasonable, therefore, to imagine that constitutional factors might concomitantly affect both properties, since sickling of erythrocytes occurs for the most part among Negroes. In support of this idea was the suggestion made by Josephs [12] that further study of the disease from the standpoint of agglutination should be made, as well as the report by Huck and Guthrie,[38] who found anomalous iso-agglutinins in a patient with sickle cell anemia. An added stimulus to this method of study was the suggestion made by Landsteiner [40] of the possibility of an immune agglutinogen in sickle cell anemia as a result of the work of Guthrie. Since Landsteiner [41] and Wiener [42] have already shown that the immune agglutinogens M and N are inheritable properties of red blood cells, the inclusion in this work of their method of study of these immune properties and of applying them to sickle cells is feasible. Another reason why this phase of study particularly applies here was given in the report by Landsteiner [43] that he had found a specific racial agglutinogen in specimens of Negro blood. Investigation of this agglutinogen was intended at first, but because of technical difficulties the idea had to be abandoned, and the study was confined to iso-agglutinogens and the immune factors M and N.

PROCEDURE

Patients whose red blood cells showed the sickling trait were located among those in the wards and in the clinic of the Provident and the Cook County Hospital by testing them as a routine when blood was being drawn for Wassermann tests. One drop of the blood collected in the syringe was placed in 2 cc. of physiologic solution of sodium chloride. This suspension was used for typing the cells. Next the third finger of the left hand was cleansed with alcohol and pricked. A drop of this blood was used to make the test for sickling. The first 800 patients were tested by the well known cover glass and slide method. For the remaining tests in the total series the "standardizing sickle cell method" of Beck and Hertz [2] was used in addition to the other method. The cover glass was "ringed" with melted petrolatum which had first been drawn into a large medicine dropper. The dropper was passed through a flame as needed when the petrolatum did not flow easily. The slides were placed horizontally in a closed cabinet at room temperature and examined under the microscope the next morning.

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40. Landsteiner, K.: Personal communication to Dr. Julian H. Lewis, of the University of Chicago.

41. Landsteiner, K., and Levine, P.: Individual Differences in Human Blood, J. Exper. Med. **47**:757 (May) 1928.

42. Wiener, A. S.: Determination of Non-Paternity by Means of Blood Groups, Am. J. M. Sc. **186**:257 (Aug.) 1933.

43. Landsteiner, K.; Strutton, W. R., and Chase, M. W.: An Agglutination Reaction Observed with Some Human Bloods, Chiefly Among Negroes, J. Immunol. **27**:469 (Nov.) 1934.

The suspension of cells collected in physiologic solution of sodium chloride from each patient was typed, anti-A and anti-B serums prepared and standardized [44] in the laboratory being used. The standard laboratory technic for determining blood types was used. Examination of the mixture of cell suspension and serum was made both microscopically and macroscopically.

Every case of sickling encountered was rechecked at least once with a newly drawn specimen of blood. A double check on all the tests was possible when the Beck and Hertz method was included in the testing along with the cover slip method. In performing the Beck and Hertz test, 1 drop of the blood to be tested was added to a small test tube containing 1 cc. of equal parts of physiologic solution of sodium chloride and 3 per cent solution of sodium citrate. After the blood was added the suspension was overlayed with liquid petrolatum, and the tube was allowed to stand overnight at room temperature. It was found, after a series of trials in known cases in which the results were occasionally inconsistent, that the saline-citrate solution must be acidified to a p_H of 6.9 (colorimetric method) to obtain consistently satisfactory results.[45] Before the slide preparations were examined microscopically each morning, 0.5 cc. of neutralized solution of formaldehyde was added beneath the layer of liquid petrolatum in each tube containing the saline-citrate suspension. The formaldehyde fixed the cells in whatever shape they had assumed, and after the slide preparation had been examined a drop of the cell suspension was withdrawn from beneath the layer of liquid petrolatum, placed under the microscope and examined for sickle cells.

For the preparation of the anti-M and the anti-N serums the Landsteiner technic [41] was followed completely, with the exception of the method for testing the unknown specimens of blood. To avoid possible conflicting results because of the agglutinogen P in Negroes, only the immune serums produced by the injection of type O cells from white patients were used for routine testing. The immune serums obtained by the injection of blood from normal Negroes and from patients who showed sickling were used in special tests.

Since 20 or 30 specimens of blood were examined at one time, it was found more practical to substitute the Wiener [46] centrifugation method for the slide method of Landsteiner when testing for M and N agglutinogens. For each batch of blood studied, known specimens of M and N blood were used as controls. All the recordings of the results were made only as plus or minus.

The specimens of blood injected into rabbits were specimens for which the type either had been previously determined through the courtesy of Dr. Wiener or had been determined with absorbed serums furnished by him.

INCIDENCE OF SICKLING

Present Findings.—The patients on whom these studies were made were found in the clinic and the wards of the Provident Hospital and the wards of the Children's Hospital and the men's medical wards of the Cook County Hospital. A total of 1,263 Negroes were tested. This

44. Coca, A. F.: Slide Method of Titrating Blood-Grouping Sera, J. Lab. & Clin. Med. **16**:405 (Jan.) 1931.

45. Suggestions received from Dr. Beck, through personal correspondence, were of assistance on this particular point.

46. Wiener, A. S.; Zinsher, R., and Selkowe, J.: The Agglutinogens M and N of Landsteiner and Levine, J. Immunol. **27**:431 (Nov.) 1934.

Fig. 1.—Photomicrograph of the sickle cells of a Mexican boy aged 9 years. The Beck and Hertz method was used, and the cells were fixed in solution of formaldehyde. Magnification, 1,000.

number included 278 children under 15 years of age and 985 adults. Of this number, 119 (9.42 per cent) were found to have erythrocytes that "sickled" when tested, as indicated in the procedure. One patient, or 0.32 per cent, of the 307 non-Negroes tested showed sickling (fig. 1). In the latter group there were 189 children under 15 years and 118 adults. A complete summary of patients tested is found in table 1.

TABLE 1.—*Summary of Data for Patients Tested for Sickling*

Negroes tested		
A. Negative results		
Adults	899	
Children	244	
Total		1,143
B. Positive results		
Adults	86*	
Children	34	
Total		120
Total Negroes tested		1,263
Percentage of positive results among Negroes, 9.42		
Non-Negroes tested †		
A. Negative results		
Adults	118	
Children	188	
Total		306
B. Positive results		
Adults	0	
Children	1‡	
Total		1
Total non-Negroes tested		307
Percentage of positive results among non-Negroes, 0.32		
Grand total of patients tested		1,570

* Includes a female showing "elliptical-shaped" red blood cells (fig. 2).
† Includes Nordics, Mexicans, Greeks, Italians, Spanish, Filipinos, Chinese and others (see table 3).
‡ A Mexican boy aged 10 years (fig.1). One patient other than the 1 listed here (a white male of Irish extraction) showed peculiarly shaped cells unlike any described in the literature (fig. 3). Numerous subsequent tests, after the first, failed to show the same type of cells. He is, therefore, listed in the group showing negative results.

Each person whose red blood cells show the sickling phenomena is not necessarily anemic. As a matter of fact the great majority of those who showed sickling had a normal red cell count, a normal hemoglobin value, no reticulocytosis and no evidences of blood destruction at the time the blood was tested. Some authors call such a condition latent sickle cell anemia, and Cooley [47] has suggested that it be called "sicklemia," simply to indicate that the erythrocytes undergo the deformity. Only those persons who have all the signs and symptoms of

47. Cooley, T. B., and Lee, P.: The Sickle Cell Phenomenon, Am. J. Dis. Child. **32**:334 (Sept.) 1926.

anemia together with the laboratory evidence, including the characteristic poikilocytosis, should be considered to have sickle cell anemia. It is generally believed, however, that every patient with "sicklemia" is potentially "anemic," although the factor that causes this regression is not definitely known. Similarly, it is believed that a person who is "anemic" may revert to the nonanemic phase.

Incidence of Sickling Reported by Previous Investigators.—There is nothing in the literature whereby one may conclude from the incidence of the sickling phenomena what percentage of those in one phase of the disease may revert to the other. About all that can be assumed is that each person with sicklemia is potentially anemic and as such offers a medical problem. The incidence of those whose cells sickled, without

TABLE 2.—*Comparison of Percentages of Patients with Sickling Among a Large Series of Negroes Tested by Various Investigators* *

Investigators	Number of Patients Tested	Number of Positive Results	Percentage of Positive Results
Cooley and Lee [47]	400	30	7.50
Levy [44]	213	12	5.60
Graham and McCarty [11]	858	58	6.75
Josephs [12]	250	16	6.40
Diggs [36]	827	68	8.20
Miyamoto and Korb [14] †	300	19	6.30
Present series	1,263	119‡	9.42
Total	4,111	322	7.83

* Data published by investigators who have reported positive results in various communities without giving the number of persons examined or who have examined only non-Negro subjects have been omitted from this table.

† These investigators have also tested non-Negroes, but the data are not included in this chart.

‡ This number does not include 1 positive result for a non-Negro (Mexican) and for a Negro having so-called elliptical-shaped cells.

regard to the presence of anemia, is shown in table 2, where the findings of previous investigators for a large series of Negroes are listed. The number of tests made (1,263) and the series of patients (119) showing sickling reported in this paper are larger than any other included in the chart. Because of the large number of tests, the results should more accurately approach the actual incidence of the sickling phenomena. As over 4,000 Negroes have been tested, when the present work is included, an average incidence is determined and found to be 7.83 per cent. This percentage may, presumably, be considered as the average "sickling" expectancy for the entire Negro population in America.

Distribution of Cases Among Non-Negroes.—Only three reports of a large series of tests on non-Negroes are found in the literature. Sydenstricker [7] found no sickling among non-Negroes in Georgia after 300 tests. Miyamoto [14] obtained similar results for 100 non-Negroes he tested in St. Louis, while Wallace [26] tested 139 Mexican children and

100 Mexican adults, with 3 positive results. The 3 patients who showed sickling were all children of the same family. Lawrence [48] has reported 3 positive results for 102 non-Negroes tested, but the pictures he presented of the blood cells in his article have been criticized as not being "sickle cells" but "elliptical cells," and he has since reported them as of that type. Many isolated reports of sickling of the erythrocytes in

TABLE 3.—*Nationalities of Patients Tested**

		No. of Patients
Born in the United States		
Negro		1,263
Non-Negro		145
Foreign born		
Austria	7	
Bohemia	2	
Canada	3	
China	3	
Czechoslovakia	6	
England	3	
Finland	1	
France	1	
Germany	17	
Greece	2	
Hungary	4	
Ireland	10	
Italy	30	
Jugo-Slavia	4	
Lithuania	15	
Mexico	12	
Persia	1	
Philippine Islands	2	
Poland	19	
Rumania	1	
Russia	12	
Scotland	1	
Spain	1	
Sweden	2	
Switzerland	2	
Wales	1	
Total		162
Grand total		1,570

* In the case of children the nationality is taken as that of the father or mother when either was born outside the United States and that of the father when both were born outside the United States.

Jews, Americans and Italians have appeared in the literature since Cooley [18] reported sickling in a Greek child. Since Cooley [49] has expressed the opinion that routine tests for sickle cells should be made not only for Negroes but also for those of Mediterranean ancestry as well, the nationalities of the 307 non-Negroes reported on in this paper are shown in table 3.

48. Lawrence, J. S.: Elliptical and Sickle-Shaped Erythrocytes in Circulating Blood of White Persons, J. Clin. Investigation **5**:31 (Dec.) 1927.

49. Cooley, T. B., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 3, chap. 16, p. 37.

BIZARRE FORMS ENCOUNTERED

In the course of the testing of those patients whose cells sickled, 2 persons were found whose cells were bizarre and yet could not be considered sickle cells. The first patient, who had "elliptical-shaped cells" (fig. 2), was a 65 year old, very dark Negro woman, a member of a family of 9, none of whom lived in Chicago and who were therefore not tested. Patients having similar blood findings have been reported by Dresbach,[50] Hunter,[51] Lawrence [52] and Terry.[53] Terry has

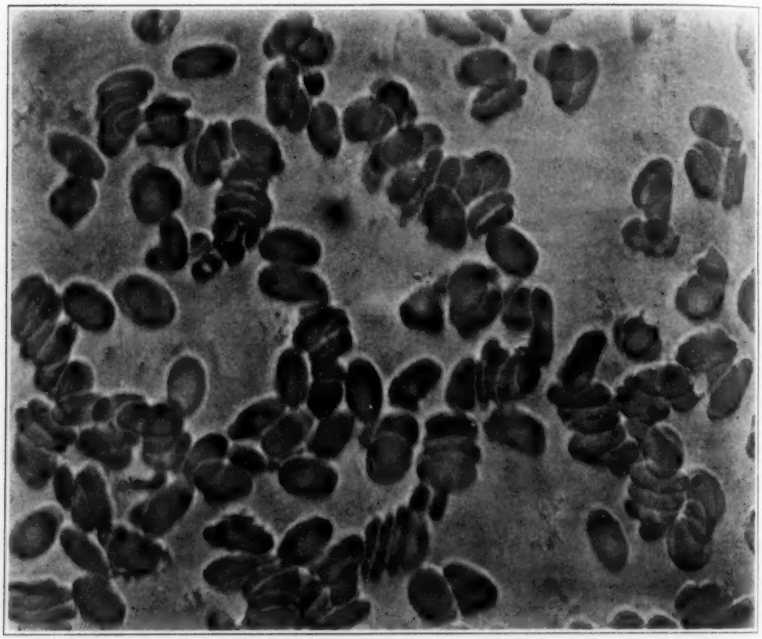

Fig. 2.—Photomicrograph of "elliptic" cells of a 65 year old Negress. The cells are shown to demonstrate the contrast between those in figures 1 and 3. Magnification, 750.

50. Dresbach, M.: Elliptical Human Red Corpuscles, Science **19**:469, 1904; Elliptical Human Erythrocytes, ibid. **21**:473, 1905.

51. Hunter, W. C., and Adams, R. B.: Hematologic Study of Three Generations of a White Family Showing Elliptical Erythrocytes, Ann. Int. Med. **2**:1162 (May) 1929; A Further Study of a White Family Showing Elliptical Erythrocytes, ibid. **6**:775 (Dec.) 1932.

52. Lawrence, J. S.: Human Elliptical Erythrocytes, Am. J. M. Sc. **181**: 240 (Feb.) 1931.

53. Terry, M. C.; Hollingsworth, E. W., and Eugenio, V.: Elliptical Human Erythrocytes: Report of Two Cases, Arch. Path. **13**:193 (Feb.) 1932.

collected reports of 52 cases and has found the patients to be equally divided between Negroes and non-Negroes and as to sex. A photograph (fig. 3) of a camera lucida drawing of the peculiarly shaped cells present in the blood of the Irish boy referred to in table 1 shows the cells of the second patient. A total of 14 separate tests were made for the patient, with 2 or 3 smears each time. Twelve of these tests were checked by the Beck and Hertz method. When first tested, the patient was toxic. The diagnosis at this time was "bilateral otitis media" and "nephritis." Later there developed marked swelling of the joints with exquisite pain, and the final diagnosis was "chronic rheumatoid arthritis."

Fig. 3.—Photograph of a camera lucida drawing of cells of a 13 year old non-Negro of Irish extraction, referred to in table 1. Note the contrast between these cells and the typical sickle cells shown in figure 1. This drawing was made by Dr. Katsuji Kato, of the University of Chicago, at table level using a no. 10 ocular and an oil immersion lens.

Subsequent tests showed that the patient was less toxic, though his temperature continued to be elevated. The peculiarly shaped cells were seen when the child was first tested. Their shape was noted about fourteen hours after the cover slip preparation had been made. It was estimated that about 95 per cent of the cells had assumed the odd shape. An accurate word picture is, of course, somewhat inadequate, but the cells may be described as having a very small biconvex round center, about one-third the diameter of a normal red blood cell, densely packed with hemoglobin. At diametrically opposite points on the circumference of the center, long, fine spearlike processes protruded. The length of each of these processes was about twice the diameter of a

normal erythrocyte. They were almost totally transparent, except for a streak of hemoglobin that extended from the central mass to the pointed tip. These elongations did not bend from side to side as the cells were made to jostle against each other by slight pressure with the lens against the cover slip. The camera lucida drawing shown here (fig. 3) was made about forty-eight hours after the cells were first observed. Within about seventy-two hours a large majority of these erythrocytes had returned to the spherical form, and all had become round biconcave disks within five days. At no time did any of the cells have the characteristic sickle cell shape. All agglutinating reactions of both of these patients were normal.

Cooley [54] has considered the effect on the red blood cells of many infectious states and has presented drawings of the various shapes the cells may take. He has called these shapes "degrees of fragmentation" and has stated that he thinks the simplest explanation would be that "the toxins of the infection affect the marrow in such a way as to cause the production of defective cells which break down easily." He has stated that "fragmentation" can best be seen in moist films. Auer [55] has studied the structure and function of filaments produced by living red blood corpuscles and has given various examples of the shapes taken when red blood cells of human beings and animals are used. Oliver [56] has similarly studied the processes produced by human erythrocytes and has presented a method of staining them. The oddly shaped cells previously mentioned did not resemble those described by Cooley with respect to shape and the fact that they returned to the normal form instead of disintegrating while in the irregular form. They did, however, appear like some of the irregularly shaped erythrocytes described by Auer. Apparently no other explanation than the toxicity of the patient fits the reason for the alteration in the shape of the corpuscles. If this is the case, such a picture might be expected in other toxic states if tests were made to detect them.

DISTRIBUTION OF AGGLUTINOGENS O, A, B AND AB

With the exception of the work reported by Huck [8] there is no information on the distribution of the blood groups of those persons whose red blood corpuscles sickle. Using the Moss classification, Huck found that the 14 patients of his series who showed sickling were distributed

54. Cooley,[49] p. 4.

55. Auer, J.: The Structure and Function of Filaments Produced by Living Red Corpuscles, Am. J. M. Sc. **186**:776 (Dec.) 1933.

56. Oliver, W. W.: Staining the Processes (Flagella) of Human Erythrocytes, J. Infect. Dis. **55**:267 (Nov.-Dec.) 1934.

as follows: 4 in group IV (type O); 3 in group II (type A); 4 in group III (type B) and 1 in group I (type AB). One patient he was unable to include in either of these groups because of peculiar agglutinating reactions. He made no comparison between the grouping of the patients and that of normal Negroes.

The work reported herein includes a determination of the blood type of 1,560 persons. The blood of only 10 of the patients tested for sickling was not typed. The data obtained from these blood typings was divided into three main parts, each having the four known blood groups, O, A, B and AB. The first part was composed of the non-Negroes whose erythrocytes did not show sickling (normal non-Negroes); those composing the second part were Negroes whose cells likewise showed no sickling (normal Negroes); the third part included

TABLE 4.—*Distribution of Agglutinogens O, A, B and AB*

Type	Normal Non-Negroes		Normal Negroes		Patients with Sickling*	
	Number	Percentage	Number	Percentage	Number	Percentage
O (I)	151	49.34	580	51.19	65	53.71
A (II)	97	31.69	279	24.62	32	26.44
B (III)	40	13.07	224	19.77	18	14.87
AB (IV)	18	5.88	50	4.41	6	4.95
Unknown†	..		10		..	
Total	306		1,143		121	

* Includes 1 non-Negro (Mexican) of type O and 1 Negro with so-called elliptical cells, type O.

† These patients were tested for sickling, but no blood was obtained for typing.

the Negroes and the single non-Negro whose red blood corpuscles showed the sickling phenomena. The numerical and the percentage distribution of each blood type in each part is shown in table 4.

Anomalous Iso-Agglutinins in Patients Showing Sickling.—No difficulty was encountered in the routine typing of the blood, although Huck did find 1 patient whom he could not include in either of the four groups. In collaboration with Guthrie, Huck [38] has reported another case, that of a patient whose cells sickled and who also showed anomalous agglutinating reactions. They found that the washed red blood corpuscles of the patient belonged in group III Moss (type B) but the serum belonged in group I (type AB). To recheck these irregular results the cells and the serum of the patient were cross-matched against those of 59 persons whose blood was distributed among the four known groups. The same end-results were obtained in each case. The family of the patient was next investigated for similar anomalous reactions, and the chart for the family is reproduced here. The original patient was C. T.

From this chart it will be seen that the red blood cells of the patient's mother, father and 2 sisters showed sickling. One of these sisters and a brother, whose cells were normal, had questionable blood types, like that of C. T. The sister with the anomalous blood type married a man with normal red blood corpuscles of group I (type AB). From this union there were 2 boys with normal erythrocytes, 1 girl who had sickle cells but whose blood was of normal type and 1 with normal red blood cells but an anomalous blood type, like that of her mother and her aunt. These authors were able to find 13 specimens from the 142 persons tested that were agglutinated by the serum of patient C. T. Each of these specimens was of type II. Guthrie and Huck did not state how many of the specimens that were agglutinated showed sickle cells or how many persons had serum that did not normally corre-

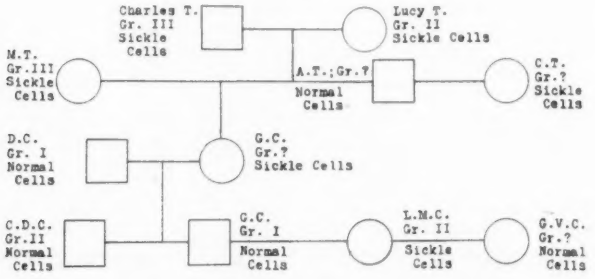

Fig. 4.—Chart of the family of patient C. T.

spond to the cell type, as was the case with their original patient. From their evidence the authors said they thought they had found a fifth isohemo-agglutinin to add to the four already known.

Since the anomalous agglutinins found by Guthrie and Huck were in blood containing sickle cells, the possibility of similar irregular reactions was considered in the series reported in this paper. Accordingly, 440 cross-matchings were made, washed cells and inactivated serum of patients with known sickle cells and the washed cells and inactivated serum of normal Negroes and of non-Negroes being used. The results are shown in tables 5 to 8. No reactions of any kind resembling those reported by Huck and Guthrie were found. In fact, all the reactions were those normally to be expected when fresh cells and serums are used. The one irregularity noted occurred when the cells were preserved [57] too long in the refrigerator.

57. Rous, P., and Turner, J. R.: The Preservation of Living Red Blood Cells in Vitro, J. Exper. Med. **23**:219 (Feb.) 1916.

DISTRIBUTION OF AGGLUTINOGENS M, N AND MN

In 1901 Landsteiner [58] definitely proved the theory he had presented the year before that the blood of the human race can be divided into three separate and distinct groups. The fourth group was discovered a year later by von Decastello and others.[59] This division of human

TABLE 5.—*Cross-Matching of Washed Sickle Cells Against Inactivated Serums of Patients Showing Sickling*

		Sickle Cell Serum							
Sickle Cells	Type	S 33 Type O	S 749 Type O	S 759 Type A	S 872 Type AB	S 979 Type B	S 981 Type A	S 1020 Type O	S 1057 Type A
S 33	O	—	—	—	—	—	—	—	—
S 749	O	—	—	—	—	—	—	—	—
S 759	A	+	+	—	—	+	—	+	—
S 872	AB	+	+	+	—	+	+	+	+
S 979	B	+	+	+	—	—	+	+	+
S 981	A	+	+	—	—	+	—	+	—
S 1020	O	—	—	—	—	—	—	—	—
S 1053*	A	+	+	—	—	+	—	+	—
S 1054*	O	—	—	—	—	—	—	—	—
S 1055*	O	—	—	—	—	—	—	—	—
S 1056*	A	+	+	—	—	+	—	+	—
S 1057*	A	+	+	—	—	+	—	+	—
S 385	O	—	—	—	—	—	—	—	—

* These patients were all members of the same family. S 1053 was the mother.

TABLE 6.—*Cross-Matching of Normal Washed Red Blood Cells of Non-Negroes and Negroes Against Inactivated Sickle Cell Serum* *

		Sickle Cell Serum											
Cells	Type	33 O	749 O	759 A	872 AB	877 B	878 AB	979 B	981 A	1020 O	263 O	691 B	110 A	1018 O
N 860	O	..	..	—	..	—	—	..	..	..	—	—	..	..
N 950	A	+	..	—	..	+	—	..	..	..	+	+	..	..
N 858	B	+	..	+	—	—	—	—	+	+	+	—	+	+
N 963	O	—	..	..	—	..	..	—	—	—	..	—	—	—
N 938	A	+	..	..	—	..	..	+	—	+	..	+	—	+
N 952	A	+	..	..	—	..	..	+	—	+	..	+	—	+
N 1017	A	+	..	..	—	..	..	+	—	+	..	+	—	+
W 4	O	—	—	..	—	..	..	—	—	—	..	..	..	—
W 8	O	—	—	..	—	..	..	—	—	—	..	..	..	—
W 21	O	—	—	..	—	..	..	—	—	—	..	..	..	—
W 26	B	+	+	..	—	..	..	—	+	+	..	..	..	+
W 27	B	+	+	..	—	..	..	—	+	+	..	..	..	+
W 30	A	+	+	..	—	..	..	+	—	+	..	..	..	+
W 32	B	+	+	..	—	..	..	—	+	+	..	..	..	+
W 34	O	—	—	..	—	..	..	—	—	—	..	..	..	—
N 948	O	—	..	..	—	..	..	—	—	—	..	—	—	—

* N refers to cells of Negro patients; W refers to cells of non-Negro patients.

bloods into the four now well known groups was based on properties found in the cells (agglutinogens) and a corresponding factor in the

58. Landsteiner, K.: Ueber Agglutinationserscheinungen normalen menschlichen Blutes, Wien. klin. Wchnschr. **14**:1132, 1901.

59. von Decastello, A., and others: Ueber die Isoagglutine im Serum gesunder und kranker Menschen, München. med. Wchnschr. **49**:1090, 1902.

serum (agglutinin). Since the announcement of this first discovery, Landsteiner [41] has shown that by means of an immune serum from rabbits, produced by the injection into these animals of human cells,

TABLE 7.—*Cross-Matching of Washed Sickle Cells Against Inactivated Serums of Normal Negroes*

		Normal Serums of Negroes							
Sickle Cells	Type	N 860 Type O	N 950 Type A	N 858 Type B	N 880 Type AB	N 938 Type A	N 948 Type O	N 953 Type O	N 1017 Type A
S 33	O	..	..	—	..	—	—	—	—
S 263	O	—	—	—	—	..	..	..	..
S 385	O	—	—	—	—	—	—	—	—
S 691	B	+	+	—	—	+	+	+	..
S 749	O	—	—	—	—	—	—	—	..
S 759	A	+	—	+	—	—	+	+	—
S 872	AB	+	+	+	—	+	+	+	+
S 877	B	+	+	—*	—	+	+	+	..
S 878	AB	+	+	+†	—	+	+	+	..
S 979	B	+	+	—	—	+	+	+	+
S 981	A	+	—	+	—	—	+	+	—
S 1018	O	—	—	—	—	—	—	—	—
S 1020	O	—	—	—	—	—	—	—	—
S 1053‡	A	..	..	+	..	—	+	..	—
S 1054‡	O	..	..	—	..	—	—	..	—
S 1055‡	O	..	..	—	..	—	—	..	—
S 1056‡	A	..	..	+	..	—	+	..	—
S 1057‡	A	..	..	+	..	—	+	..	—

* After being preserved for one month these same cells when tested against the same serum were agglutinated. The cells reacted similarly against type III (B) commercial serum.
† After being preserved for one month these same cells when tested against the same serum failed to agglutinate. No agglutination occurred with type III (B) commercial serum; there was agglutination with type II (A) serum.
‡ The same family noted in table 5.

TABLE 8.—*Cross-Matching of Washed Sickle Cells Against Inactivated Serums of Normal Non-Negroes*

		Normal Serums of Non-Negroes						
Sickle Cells	Type	W 2 Type B	W 8 Type O	W 10 Type B	W 25 Type O	W 26 Type B	W 27 Type B	W 30 Type A
S 33	O	—	—	—	—	—	—	—
S 385	O	—	—	—	—	—	—	—
S 749	O	—	±*	±*	—	—	±*	—
S 759	A	+	+	+	+	+	+	—
S 878	AB	—†	..	—†	..	—†	—†	+†
S 979	B	—	+	—	+	—	—	+
S 981	A	+	+	+	+	+	+	—
S 1018	O	—	—	—	—	—	—	—
S 1020	O	—	—	—	—	—	—	—
S 1053‡	A	+	+	+	+	+	+	—
S 1054‡	O	—	—	—	—	—	—	—
S 1055‡	O	—	—	—	—	—	—	—
S 1056‡	A	+	+	+	+	+	+	—
S 1057‡	A	+	+	+	+	+	+	—
S 872	AB	+	+	+	+	+	+	+

* These cells had been kept in a preservative for one month when tested. When rechecked with fresh cells, all the reactions were normal.
† See note for same cells in table 7.
‡ Same family noted in table 5.

he could demonstrate even other agglutinable properties in erythrocytes for which there were no normal corresponding agglutinins in human serum. These new agglutinogens have been designated M, N and MN. Landsteiner has produced evidence to show that these factors are

inheritable mendelian dominants, and he has discussed a theory according to which the inheritance of the new agglutinogens depends on a single pair of allelomorphic genes. He [43] has shown further that another immune agglutinogen, in addition to those mentioned, is present in the cells of Negroes, and he has stated the belief that this property, which he has called agglutinogen P, is specific for that race. He suspects that with proper technic even other agglutinogens may be demonstrated in red blood cells. No application of the principle of the immune agglutinogens to the erythrocytes having the sickling trait has thus far been reported.

Using the technic outlined by Landsteiner, with the substitution of the centrifugation method for testing described by Wiener, previously mentioned in the procedure, specimens of the blood of 306 normal non-Negroes, 209 normal Negroes and 63 patients with positive sickle cells

TABLE 9.—*Distribution of Agglutinogens M, N and MN*

Type	Normal Non-Negroes		Normal Negroes		Positive Results*	
	Number	Percentage	Number	Percentage	Number	Percentage
M	97	31.69	61	29.18	20	31.74
N	64	20.91	56	26.79	16	25.39
MN	145	47.38	92	44.01	27	42.85
Total	306		209		63	

* Includes 1 non-Negro (Mexican), type MN, and 1 Negro showing so-called elliptical cells, type MN.

were typed with anti-M and anti-N immune serums. The numerical and percentage distributions of M, N and MN for each of these three groups are shown in table 9.

On examination of table 9, no striking differences in the percentage distribution of either of the three combinations of agglutinogens is noted in any of the three groups of persons studied. The percentage distribution of agglutinogen N is somewhat higher among the normal Negroes and the group showing sickling, but whether this variation is significant racially needs further statistical verification.

ATTEMPT TO DETERMINE A SPECIFIC AGGLUTININ

Since no significant percentage variation was obtained when testing for M and N, a further effort was made to detect anomalous immune agglutinogens. Three immune serums, AM, ON and ABMN, produced from the blood of patients with sickle cells (2 were anemic and in the hospital at the time the blood was drawn for injection into rabbits) were separately absorbed with washed cells from white patients having the same blood type (normal and immune types). To eliminate as far as possible the blood of persons having possible intermixture

with whites, only the blood of very dark-skinned Negroes was chosen to produce the serum. The completely absorbed serum was tested against the cell suspension of 30 specimens of blood of unknown type and from patients of both races collected fresh that day. No agglutination of any of these cells or of any of the control cells occurred. The same procedure was repeated on two other occasions, fresh suspensions of unknown cells being used. No agglutination of the completely absorbed serum has ever occurred. To detect further any specific immune property possibly present in the prepared serum, each specimen was tested against the cells of 12 patients who showed various types of sickling. These cells had been kept in a refrigerator suspended in the preservative already referred to but had been washed before using. Again, no agglutination occurred with the control cells or the sickle cells. From these results it is apparent that with the methods used no specific immune agglutinin was produced in the rabbit serum with the particular sickle cells used. It should be noted, however, that at the time of the injection the cells were not actually "sickled," since none of the cells having the deformity will remain that way when exposed to air.

FACTORS IN THE SICKLING PHENOMENA

With so many specimens of blood available from persons whose cells were known to sickle, some attempt was made to study the question: Would these cells undergo their characteristic deformity in the absence of serum? For, as has been shown, Huck and Hahn individually presented evidence that serum was not needed, while Sydenstricker and Josephs have, separately, taken the opposite view. On the publication by Beck and Hertz[2] of a new procedure for testing for sickle cells, an excellent method was available whereby this theory could be studied. This method consists, to repeat briefly, of a saline-citrate suspension of the suspected cells overlaid with liquid petrolatum. After from twelve to twenty-four hours the cells are fixed in whatever form they may have assumed with neutral solution of formaldehyde and then examined microscopically. With this new technic four different experiments were devised for investigating the problem.

The first attempt at investigating was divided into two parts. Part one consisted of a repetition of the work of the aforementioned four authors on freshly drawn and washed cells with and without serum. By using the Beck and Hertz technic it was found that sickling of the cells occurred in approximately the same percentage in the tube containing no serum as it did in the tube having serum. Since it has not been specifically shown that only freshly drawn and washed cells must be used, it was decided that the second part of this phase of the study should be the inclusion of preserved cells of patients known

to show sickling, with the same technic as before. The results here paralleled the previous ones—sickling occurred just as well in the tube with serum as in the one without it. Care had been taken to determine whether the preserved cells had sickled while standing in the refrigerator. These results are shown in table 10. The percentages given in this chart for the two types of cells were determined by microscopic study of stained smears of the fixed cells.

By substituting plasma from normal Negroes for the serum in the foregoing test, the second test of the theory of these investigators was

TABLE 10.—*Test 1: Effect of Sickling Phenomena of Fresh and Preserved Sickle Cells With and Without Sickle Cell Serum (Inactivated)* *

	Washed Sickle Cells†															
	Part 1				Part 2											
	S 1018 Type O		S 1020 Type O		S 979 Type B		S 981 Type A		S 749 Type O		S 872 Type AB		S 691 Type B		S 33 Type O	
	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution
Sickle and bizarre forms, percentage....	73	77	93	90	52	64	17	19	3	11	35	46	6	9	44	59
Round and crenated forms, percentage....	27	23	7	10	48	36	83	81	97	89	65	60	94	91	56	41

* The solution used by Beck and Hertz consists of equal parts of physiologic solution of sodium chloride plus 3 per cent solution of sodium citrate at p_H 6.9. For the controls, the Beck and Hertz solution plus washed sickle cells was used.

† For S 1018 and S 1020 the cells were freshly drawn and washed in saline solution. For S 979 and S 981 the cells were kept in Locke's solution in the icebox for two weeks and washed in saline solution before being used. For S 749 the cells were kept in Locke's solution in the icebox for one month and washed in saline solution before being used. For S 872, S 691 and S 33 the cells were kept in Locke's solution in the icebox for seven weeks and washed in saline solution before being used.

made. As in the previous test, sickling occurred in the tube without plasma as well as in the one with it. Similar results were obtained with the third test when serum from normal white patients was used in place of the plasma. The characteristic poikilocytosis occurred in each tube. These results are shown in tables 11 and 12.

No chart is presented for the fourth test, since in each instance (control and testing tube) no sickling occurred when inactivated serum from patients who showed sickle cells was added to the saline-citrate suspension of cells from normal non-Negroes and Negroes.

Each of these tests shows that red blood cells having the sickling trait do not require the presence of either serum or plasma to assume their characteristic form. Further, test 1 (table 10) shows that whatever the factor may be that causes the cell to sickle, it remains within

the cell and under appropriate circumstances will exert itself as long as the cell remains intact. This last observation, as far as is known, is not reported in previous literature.

Agglutination and the Sickling Phenomena.—The tests just presented have suggested another study that might be undertaken. Would cells having the sickling tendency undergo this deformity after they had been agglutinated? With a fresh suspension of red blood cells of a patient with known sickling, type A-M, anti-A commercial serum was added to agglutinate the cells in a small test tube. The mixture of serum and cells was allowed to stand fifteen minutes to be sure that agglutination had occurred. As a control, a drop of the mixture was watched microscopically for clumping. When agglutination was

TABLE 11.—*Test 2: Effect of Plasma from Normal Negro Patients on Sickling Phenomena of Washed Sickle Cells**

	Washed Sickle Cells									
	S 979 Type B		S 1018 Type O		S 1020 Type O		S 749 Type O		S 872 Type AB	
	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Only	0.1 Cc. of Serum and B. & H. Solution
Sickled and bizarre forms...	+++	+++	++++	+++	+++	+++	++	+	++++	++++
Round and crenated forms....	Few	Few	Few	Few	Few	Few	Moderate	Many	Few	Few

* 1 plus indicates an estimated 25 per cent; 2 plus, 50 per cent; 3 plus, 75 per cent, and 4 plus, 100 per cent. The ages of the cells and the description of the controls were the same as given in table 10.

definite the cell suspension in the tube was overlaid with liquid petrolatum and permitted to stand over night. In accordance with the Beck and Hertz technic, these cells were examined the next morning, and it was found that sickling had occurred just as well in the tube containing the agglutinating serum as in the control tube having no serum. Most of the cells were no longer clumped; however, those still agglutinated were also sickled. The agglutinated cells on the glass slide, used as a control, were covered with a cover slip, and this was sealed with petrolatum. On examination the next morning it was found that the clumps had not broken up and that not more than 1 or 2 cells had sickled. No sickling was seen in the masses of agglutinated cells.

This study was continued by taking a suspension of the same cells, agglutinating them as before and then washing and centrifugating the clumps of cells with six changes of the saline-citrate solution. Between

each washing the cells were shaken for three minutes. After these washings the cells were no longer agglutinated, except for an occasional clump of two or three cells. This suspension was then overlaid with liquid petrolatum without the addition of serum, and examined the next morning by the same technic as in other tests. No sickling was noted at this time. The method was repeated with the addition of serum to one tube of the centrifugated cells and with another tube of similarly treated cells without added serum. In both instances of the repeated tests over 75 per cent sickling was obtained.

These results show that as a result of agglutination no apparent alteration in the sickling factor within the cell occurs. The 2 instances

TABLE 12.—*Test 3: Effect of Normal Serums (Inactivated) from White Patients on Sickling Phenomena of Washed Sickle Cells**

	Washed Sickle Cells									
	S 1018 Type O		S 1020 Type O		S 979 Type B		S 749 Type O		S 872 Type AB	
	B. & H. Solution; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution; Control	0.1 Cc. of Serum and B. & H. Solution	B. & H. Solution Control	0.1 Cc. of Serum and B. & H. Solution
Sickled and bizarre forms, percentage....	75	50	75	75	50	50	50	50	90	50
Round or crenated forms, percentage....	25	50	25	25	50	50	50	50	10	10

* The ages of the cells and the description of the controls are given in table 10. The percentages are approximations.

in which no sickling occurred—that of the slide preparation and that of the centrifugated cells—can conceivably be overlooked in view of the positive results obtained in the other instances in which there was complete control.

AGE, SEX AND RACE MIXTURE OF PATIENTS SHOWING SICKLING

Most reviews of the literature on sickle cell anemia summarize the age, sex, signs and symptoms and other data as they have been presented in the reports of persons having the disease. In most instances the reports are made only for patients who are definitely anemic. Anderson [5] has reviewed the literature with regard to these aspects and has graphically shown the age incidence and the frequency of the various signs and symptoms as they were reported for 49 patients with active anemia. Little information is obtainable for that group of patients commonly referred to as showing "latent sickle cell" anemia or "sicklemia."

Since the patients of this series who showed sickling were those in the active and the latent phase of the disease and since the group is probably the largest on record, a brief analysis seemed appropriate. An analysis in great detail was too formidable an undertakng, if not impossible, since almost all the patients were ambulatory and temporary hospitalization for study was prohibitive. The analysis was therefore confined to age, sex, race mixture (as estimated by objective inspection of the patient), blood and whatever clinical data were available. With the clinical data, roentgen studies and blood counts were included when made.

The age incidence of this series of patients showing sickling has been divided into ten year periods (table 13). Excluding those patients whose ages were not known, there were 62 persons under 30 years of age and 52 who were 30 years of age and over. As to the sex, 69.1 per

TABLE 13.—*Age Incidence*

Age	Number of Patients
Less than 1 year	2
1 to 9 years	19
10 to 19 years	22
20 to 29 years	19
30 to 39 years	22
40 to 49 years	15
50 to 59 years	11
60 to 69 years	4
Unknown	6
Total	120

cent were females and 30.8 per cent males. By determining the race mixture purely on the basis of color rather than type of hair, type of features and other anthropologic standards, the series consisted of 44 black persons, 60 mulattoes, 5 quadroons and 1 octoroon. Serologic determinations were performed in the hospital laboratory, and the results given here were from the first Wassermann test of the blood made for the patient. Eleven patients (9 per cent) had no records as to the Wassermann tests. Of the remaining 111 patients, 11.1 per cent showed positive results, ranging from 1 to 4 plus, while 1.8 per cent (2 patients) showed a plus-minus, or doubtful, result. Several authors [60] have reported roentgenographic changes in the bones of children found to have sickle cell anemia. For 17 of the children in this series lateral roentgenograms of the skull and long bones were made. In no instance was any bony change detected. Fifty patients of the series had at least 1 red blood cell count, a white blood cell count, a determination of the hemoglobin value (Sahli) and a reticulocyte count. To avoid unduly lengthening this report, only the erythrocyte counts and the hemoglobin values are presented. The average red

60. Moore.[30] Vogt and Diamond.[31] Brandau.[32] de Castro.[33] Grinnan.[34]

cell count was 4,200,000, and the average hemoglobin value was 86.4 per cent. Twelve of the 50 patients had counts of less than 3,000,000, and 4 had counts above 5,000,000. Clinically it appears that those patients whose erythrocytes have the sickling trait are subject to all varieties of complaints and, from the diagnostic standpoint, the same maladies commonly found among a large general clinic clientele and show no evidence of a relation of any given complaint to the sickling trait.

REPORT OF CASES

Two reports of cases are presented because of their clinical interest, in that in the adult patient active anemia was present when he was 56 years of age, and the boy with sicklemia became actively anemic and then reverted to the former nonanemic phase. This boy was the only patient of the series who had a palpable spleen.

CASE 1.—N. P., a Negro aged 56, came to the hospital on Oct. 29, 1935, with the complaint of weakness, severe headache in the frontal region, shortness of breath on exertion, precordial pain and occasional swelling of the ankles. I had previously tested him in the clinic and found marked sickling of the red blood cells. The erythrocyte count was 1,830,000; the hemoglobin value, 30 per cent (Sahli); the white blood cell count, 6,050, and the reticulocyte count, 1.4 per cent.

Past History.—The patient was born in Mississippi and moved to Buffalo, while a young man. During 1932 he was treated in the Buffalo General Hospital for "pernicious anemia" and was given liver. He has been living in Chicago for the past two years. In February 1935 he was treated at the Cook County Hospital for "partial stricture of the urethra," and after discharge he was referred to the outpatient department of Provident Hospital.

Physical Examination.—Examination revealed a very dark, emaciated man who was apparently ill. There was no evidence of icterus anywhere, and the mucous membranes were markedly pale. The spleen, liver and lymphatic glands were not palpable. There was a soft systolic murmur at the base of the heart. The blood pressure was 110 systolic and 60 diastolic. There was no cardiac enlargement.

Laboratory Examination.—When the patient was admitted to the hospital, six days after the first blood count had been made, the erythrocyte count was 1,860,000; the hemoglobin value, 40 per cent (Sahli), and the white blood cell count, 6,650. A roentgenogram of the chest was normal. The urine was normal except for a slight trace of urobilin. The van den Bergh test gave a delayed positive reaction, and the Wassermann reaction was negative.

Course.—The patient did not show fever at any time. His appetite was always good. For the first week no medication or treatment of any kind was given. At the end of this time, the red blood cell count was 2,930,000; the hemoglobin value, 55 per cent (Sahli), and the white blood cell count, 7,250. From November 12 to December 6 the patient was given 2 cc. of hog liver extract intramuscularly twice weekly. Complete blood counts were made twenty-four hours after each injection. At the end of this course of treatment, during which he was given 16 cc. of the extract, the erythrocyte count was 3,100,000; the white blood cell count, 5,900; the hemoglobin value, 65 per cent (Sahli), and the reticulocyte

count, 2.4 per cent. The patient was then discharged. He had gained 2 pounds (1 Kg.), felt well and looked much improved. He has been seen regularly each week in the clinic, at which time complete blood counts have been made. On May 27, 1936, six months after his discharge, the erythrocyte count was 3,350,000; the hemoglobin value, 85 per cent (Sahli), and the white blood cell count, 3,650. Sickling continued at from 90 to 95 per cent.

CASE 2.—R. F., a 3 year old mulatto boy, came to Provident Hospital on April 13, 1936 (for the third time since his birth there) because of a cold and

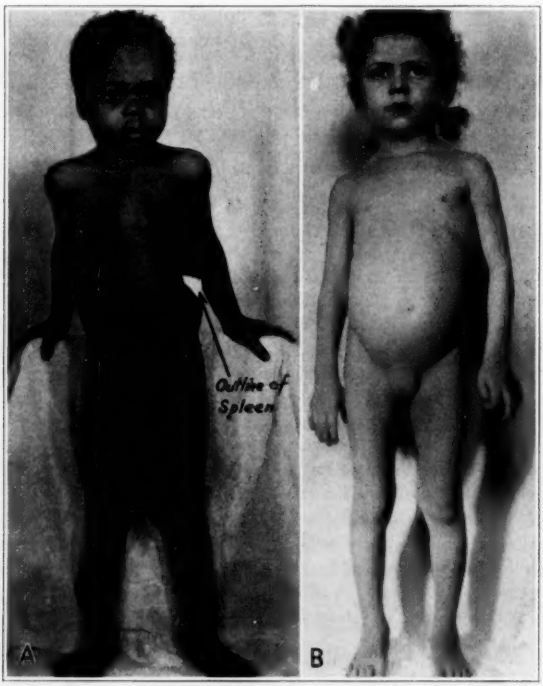

Fig. 5.—*A*, a 3 year old boy, R. F., case S 1057. When admitted to the hospital, this patient had an erythrocyte count of 1,780,000 and a hemoglobin value of 50 per cent (Sahli). Note the outline of the spleen. *B*, a 4 year old girl, J. C., case CS 270. The erythrocyte count was 3,200,000, and the hemoglobin value was 82 per cent (Sahli). Compare the color of this "creole" girl (French-Spanish-Negro blood) with that of the Negro boy (*A*).

cough, pain in the upper left portion of the abdomen and constipation. He had previously been tested in the clinic for sickling, and it was found that almost complete sickling occurred in six hours.

Past History.—The patient was born in Provident Hospital, with a birth weight of 8 pounds and 7 ounces (3,860 Gm.). He was breast fed until he was 8 months of age, when he was again admitted to the hospital, presenting a large

inguinal hernia on the left, which could not be controlled with a truss. He was operated on, and convalescence was normal. The erythrocyte counts at that time were 5,000,000 and 4,900,000, with 10,000 and 8,400 white blood cells and hemoglobin values of 85 and 80 per cent (Tallqvist). Since birth the child had been brought to the clinic frequently because of infections of the upper respiratory tract of varying severity. He was again admitted to the hospital, on June 21, 1935, when 2 years of age, with massive pneumonia involving the upper and

Fig. 6.—Photomicrograph of the sickle cells in case S 1057 (fig. 5 *A*). The "cover slip method" was used. Magnification, 750.

middle lobes of the right lung. Blood counts showed 3,500,000 and 3,950,000 erythrocytes, 20,300 and 8,000 leukocytes and 60 and 75 per cent hemoglobin (Sahli).

Family History.—The father and mother were living and well. The mother, 2 brothers and 1 sister showed sickling of the red blood cells but had no anemia. One brother and 1 sister did not show sickling. The father refused to come to the hospital for tests. There was no history of tuberculosis, syphilis, epilepsy or miscarriages.

Physical Examination.—The patient weighed 27 pounds (12 Kg.) when admitted. The nutritional state was fair. He did not appear ill. There was a profuse mucopurulent nasal discharge. There was no icterus, but the skin had a peculiar mustard-like color. The mucous membranes were markedly pale. The lymphatic glands were easily palpable in the cervical and the axillary regions. There were coarse moist râles in both lungs anteriorly and posteriorly. No dulness was noted on percussion. There were no cardiac murmurs. The spleen was palpable 1 cm. below the costal margin. There was no abdominal tenderness. The temperature was 98.6 F.

Laboratory Examination.—The blood count showed: erythrocytes, 1,780,000; hemoglobin, 50 per cent; white blood cells, 8,000, and reticulocytes 8.8 per cent. The differential count was 38 per cent polymorphonuclears, 60 per cent lymphocytes and 2 per cent monocytes. The urine was normal except for the marked presence of urobilin. The Mantoux reaction (1:10,000) was negative. Roentgenograms of the chest, long bones and skull were all normal. The icteric index was 12. There was a delayed direct van den Bergh reaction, and the Wassermann reaction was negative. Including the first count, 20 complete blood counts were made for this patient. Sternal bone marrow was studied by Dr. K. Kato, of the University of Chicago, who reported it as showing "generalized hyperplasia of all the bone-marrow elements but without an increase in any one element."

Treatment.—From April 14 to May 29, 1936, the patient was given 1 teaspoonful three times a day of a malt preparation containing 64 grains to the ounce (13 per cent) of iron and ammonium citrates. Blood counts were made twice weekly during this interval. At one time the blood count showed: erythrocytes, 3,070,000; hemoglobin, 65 per cent (Sahli); white blood cells, 11,850; reticulocytes, 8.8 per cent, and eosinophils, 9 per cent. But at the end of the course of iron a blood count showed erythrocytes, 2,220,000; hemoglobin, 55 per cent; white blood cells, 12,950, and reticulocytes, 22.1 per cent, with 8 normoblasts seen among 200 cells. The patient was then given 1 cc. intramuscularly of hog liver extract at two day intervals for four injections. Blood studies were made between injections. The patient resisted these injections strenuously. After the liver extract was stopped, the red blood count showed: erythrocytes 2,180,000; hemoglobin, 62 per cent; white blood cells, 16,950, and reticulocytes, 21.8 per cent. He was then given 2 teaspoonfuls of a commercial liver, iron and copper preparation before each meal. On June 19, when the patient was discharged, he had the same red blood cell count and hemoglobin value, but the white blood cell count had dropped to 9,100 and the reticulocyte value to 15.5 per cent.

Course.—The patient had a continuous low grade fever most of the time, and there was an occasional rise to 102 F. The infection of the upper respiratory tract was slow in clearing up. The white blood cell counts given here were high when the temperature was elevated. On discharge he had gained 1½ pounds (680 Gm.). While he was in the hospital the spleen enlarged to 4 cm. below the costal margin but gradually decreased until it was 1 cm. below the costal margin on discharge. There was no urobilin, his color had improved, the lungs were clear and the patient was active. During the summer he was taken to the country.

The patient was again admitted to the hospital, on October 19, because of a severe infection of the upper respiratory tract and abdominal pain. The blood count showed: erythrocytes, 2,000,000; leukocytes, 8,450; hemoglobin, 50 per cent (Sahli), and reticulocytes, 4.6 per cent. The spleen was still palpable about 1

inch (2.5 cm.) below the costal margin. The preparation of iron and ammonium citrates was used as before, plus 1 cc. of liver extract intramuscularly three times weekly. The patient remained in the hospital until November 12, when the blood count showed 3,240,000 erythrocytes, 10,000 leukocytes and 60 per cent (Sahli) hemoglobin. Since the patient's family is of low intelligence, he will undoubtedly return again with infections of the upper respiratory tract and perhaps severe anemia.

COMMENT

While the incidence of patients showing the sickling phenomena in this series is higher than any previously reported in the literature, as indicated in table 2, it should be noted that the number of patients tested is also larger than in any other report. The total series, however, is not entirely composed of single unrelated persons.

The inheritance of the sickling phenomena, already recognized in the literature and also shown by Huck [8] to follow the mendelian law, is well brought out in the series presented here. Forty-one of these patients represented sixteen different family groups varying from 2 to 5 members in each. In most cases there were only 2 members of the family tested, although whenever possible an attempt was made to test all the members. In no instance were both parents tested, and in most instances the father was the least inclined or accessible for tests.

The immunologic studies show that the sickling trait is apparently not confined to persons of any one of the isohemo-agglutinin or immune agglutinogen groups of which there is knowledge at present. It may still be possible that some immune property will be found in the red blood cells having this characteristic poikilocytosis.

The anomalous agglutinins found in a patient who showed sickling and in members of her family, as reported by Huck and Guthrie [38] but not found in any of the patients of the series presented here, might possibly be explained by the fact that both parents of the patient showed sickling. This postulation was not mentioned by the authors.

The tests presented in the "factors in the sickling phenomena" show conclusively that whatever the factor may be, it is inherent in the cell and not in the serum. From these tests it is apparent than any future investigative attack must be made on the cell itself and not on the serum. It may be that the protein constituents of the protoplasmic structure of the cell hold the clue.

Since no patients attending the syphilis clinic were tested, the incidence of positive Wassermann reactions among the series of patients with sickling is startling, even if it is assumed that a single report is not conclusive in all cases. At least the need for routine serologic determinations and rechecks of all positive reactions is clearly indicated. Obviously, syphilis has no part in the sickling of erythrocytes.

No satisfactory conclusion as to treatment can be drawn from the 2 case reports. While improvement was shown by the first patient as far as the erythrocyte count and hemoglobin value are concerned, one cannot, using the same standards, say the same for the second patient. In each case, however, the apparent clinical improvement based on gain in weight, increased activity, lack of complaints and general appearance was evident. On this same basis improvement has been noted among other patients treated with the same malt preparation containing massive doses of iron. Since all the laboratory work reported in this paper was done by the same person, the factor of error in each instance cannot be attributed to the variability in the technic of different persons.

CONCLUSION

A total of 1,570 patients were tested for sickling of red blood cells. The group consisted of both adults and children. There were 1,263 Negroes (9.42 per cent who showed sickling) and 307 non-Negroes (0.32 per cent).

The blood type of 1,560 of the patients tested for sickling was determined by means of the standard laboratory "slide method." The percentages of each blood group in the series of patients who showed sickling was compared with similar groups among the normal Negroes and non-Negroes. In general there was no marked tendency for the patients who showed sickling to be concentrated in any one blood group.

The distribution of the immune agglutinogens M and N was determined for 306 non-Negroes, 209 normal Negroes and 63 patients who showed sickling. The distribution of these immune agglutinogens in the patients who showed sickling corresponded, within limits, to that of the normal persons of both races.

An attempt was made to detect a specific immune agglutinogen for those who showed sickling. By the method used no specific agglutinogen was found.

The anomalous isohemo-agglutinogens which were found by another investigator in patients who showed sickling were not found in this series by cross-matching the cells and serum of patients who were known to show sickling against the cells and serum of the normal persons of both races.

Tests confirmed the work of Huck and Hahn, in which they found that serum is unnecessary in producing the sickling phenomena.

It is shown further in the same tests that the sickling factor remains within the cell, no matter how long preserved, as long as the cell itself remains intact.

Individual analysis of the entire series of 120 patients who showed sickling was made, and reports of 2 cases are given.

This project was carried out under the direction of Dr. Julian H. Lewis, of the Otho S. A. Sprague Memorial Institute, the Department of Pathology, the University of Chicago. Technical assistance was rendered in certain phases of the work by Dr. Katsuji Kato, of the University of Chicago, and many members of the staff of Provident Hospital cooperated.

Eighty-five of the Negroes and all but 5 of the non-Negroes were tested while they were in the men's medical wards and in the wards of the Children's Hospital, both of Cook County Hospital. Permission to study these patients was given by Drs. I. Pilot, R. Jaffé and M. Blatt.

NOTE.—I was unaware of work by Killingsworth [61] at the time this paper was compiled. The work herein described was completed in 1936.

426 East Fifty-First Street.

61. Killingsworth, W. P., and Wallace, S. A.: Sicklemia in Southwest, South. M. J. **29**:941 (Sept.) 1936.

PULSATIONS OF THE WALL OF THE CHEST

IV. PULSATIONS ASSOCIATED WITH ADHESIVE PERICARDIAL DISEASE

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Since the time of Skoda,[1] three pulsatory findings have been considered to be essential for the diagnosis of adhesive pericardial disease. They are: the systolic depression over the cardiac area; the diastolic cardiac thrust and the absence of the apical thrust.

Adhesions betwen the heart and the pericardium, particularly along their caudal aspect, inhibit greatly the change in shape which during systole would lead to elevation of the heart and with it to a thrust of the apical portion against the thoracic wall. Hence the apical thrust is usually absent in adhesive pericardial disease. This diagnostic finding, however, should not be evaluated too highly, because the apical thrust is often absent in the adult and, in addition to adhesive pericardial disease, there are a good number of other factors capable of diminishing or abolishing the apical thrust. Bamberger[2] has already pointed out and my colleagues and I have made the same observation that a hypertrophic heart may occasionally cause an apical thrust in spite of the presence of adhesive pericardial disease and that likewise a thrust may be caused by a right ventricle of a type which is characteristically present in disease of the mitral valve.

The systolic depression of the thoracic wall is considered to be the most important sign of adhesive pericardial disease, particularly if it is noted over a larger area (Sahli[3]) and if the ribs are included in the depression (Wenckebach[4]). One should evaluate cautiously those small localized depressions of the thoracic wall noted in the vicinity of a powerful apical thrust or taking its place when the supra-apical portion thrusts against the ribs. A systolic depression is not uncommonly found with disease of the mitral valve lateral to the area of the

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Translated by Hugo Roesler, M.D., Philadelphia.

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors.

1. Skoda, J.: Abhandlung über Perkussion und Auskultation, ed. 6, Vienna, Braumüller u. Seidel, 1864.

2. von Bamberger, H.: Lehrbuch der Krankheiten des Herzens, Vienna, W. Braumüller, 1857.

3. Sahli, H.: Lehrbuch der klinischen Untersuchungsmethoden, ed. 6, Leipzig, F. Deuticke, 1914-1920.

4. Wenckebach, K. F.: Beobachtungen bei exsudativer und adhäsiver Perikarditis, Ztschr. f. klin. Med. **71**:402, 1910.

forceful thrust of the right ventricle and over the area of the apical portion; this indicates an associated movement, and it is not justifiable to make a diagnosis of adhesive pericardial disease in these cases.

The greater majority of authors have expressed the belief that the diffuse depression of the thoracic wall in adhesive pericardial disease cannot be explained by inner adhesions only; they have claimed that outer adhesions also are a necessary prerequisite. Skoda said he thought that an inward pull of the intercostal spaces on the left was observed only in those cases in which in addition to pericardial obliteration there was fixation of the pericardium against the costal pleura. This would cause fixation of the heart against the internal wall of the chest, and the obliteration of the left pleural sinus would prevent the free shift of the lung necessary to fill in the space made vacant during systole. If, in addition, the heart (and the pericardium) were also attached to the spine, there would be observed a retraction not only of the intercostal spaces on the left but of the lower half of the sternum. A similar point of view has been expressed by Bamberger [2] and Mackenzie.[5] This opinion cannot be maintained, as is evident from a study of cases in which there was a diffuse systolic depression of the thoracic wall during life while postmortem examination revealed obliteration of the pericardial cavity only. Sacconaghi [6] has reported on such experiences, and my colleagues and I have had occasion to note similar cases.

K. J. was a woman aged 66. The clinical diagnosis in her case was concretio et accretio cordis (obliteration of the pericardial cavity with external adhesions). Postmortem examination led to a diagnosis of isolated concretio (obliteration of the pericardial cavity only). When the patient was first examined there was noted over the cardiac area a diffuse jerky pulsation, which was thought for a long time, erroneously, to be the systolic cardiac thrust. Careful correlation with the arterial pulse, however, showed that there was a diastolic propulsion of the thoracic wall which was preceded by a much less distinct systolic depression of the soft tissues and the ribs. An apical thrust was not felt. The previously mentioned pulsation was more marked on the left side in the fifth intercostal space (fig. 1*A*), but it was recognized also in the fourth intercostal space, and it extended caudad to the costal arch. Near the left midclavicular line there was noted a marked depression with a sagittal direction, while near to the sternum a shift in frontal direction, i. e., from left to right during systole, was more marked. Over the right side a similar pulsation was noted extending from the fifth rib caudad to the costal arch, with a mainly frontal direction. Here likewise the abrupt diastolic shift from left to right was much more impressive than the systolic shift. Simultaneously the ribs were slightly bowed during systole, while during diastole they underwent a flattening. The summation of the frontal movements of each half of the chest resulted in a definite pulsatory shift of the whole chest, which, as mentioned before, was more definite during diastole than during systole.

5. Mackenzie, J.: Lehrbuch der Herzkrankheiten, German translation by C. J. Rothberger, Berlin, Julius Springer, 1923.

6. Sacconaghi, G. L.: Die klinische Diagnose der Herzbeutelverwachsung (Fibrechia cordis), Leipzig, C. Kabitzsch, 1923.

On the right side cardiac dulness could not be determined by percussion because of the presence of hydrothorax. The lower sternal portion was flat. No abnormal dulness was found in the second and third intercostal spaces to the left of the sternum. On auscultation a clear first sound at the apex, reduplication of the second sound and faint sounds at the base were noted. An electrocardiogram showed a sinus rhythm, with a heart rate of 120. The blood pressure was 120 systolic and 80 diastolic. The liver extended 3 fingerbreadths beyond the costal arch in the right midclavicular line and showed a weak double-wave pulsation.

Roentgenograms showed slight enlargement of the heart. A correct determination of the size was impossible because of hydrothorax on the right.

Postmortem examination revealed that the pericardial surface was freely accessible. The epicardium and pericardium were completely fixed and inseparable; calcareous deposits were not palpated. The heart was small. The cavities of both ventricles were small. All the valves were normal.

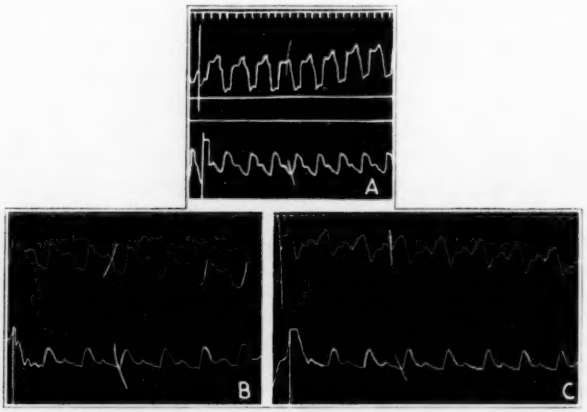

Fig. 1.—*A*, the graph demonstrates the systolic depression of the precordium in obliterative pericardial disease, without external adhesions (patient K. J.). The lower graph is for the radial artery and the upper graph for the fifth intercostal space in the left midclavicular line. The mark shows the beginning of the expulsion period. *B* and *C*, the graphs indicate the oppositely directed movement of the right and left sides of the chest, respectively, in adhesive pericardial disease (patient B. F.). In *B* the lower graph is for the radial artery and the upper graph for the fourth intercostal space in the left midclavicular line. In *C* the lower graph is for the radial artery and the upper graph for the fifth intercostal space in the right midclavicular line.

The postmortem examination in this case did not verify the clinical diagnosis of acretio (external adhesions). The heart was fixed neither to the ventral wall of the chest nor to the spine. There was noted only an obliteration of the pericardial cavity. This case demonstrates

that inner pericardial adhesions can cause a diffuse systolic depression as well as a diastolic propulsion.

Under normal conditions the aspiratory action of systole on the thoracic wall is compensated for by the opposing, centrifugal forces of the change in shape, i. e., the increase in the curvature, and, particularly, the lever movement of the heart. The presence of partial adhesions between heart and pericardium on the caudal surface of the heart is sufficient to interfere with the alteration in shape, especially the systolic lifting of the apical portion. Then the most important forces disappear which counteract the aspiration due to the reduction of the ventricular volume during the systolic efflux (miocardia), and aspiration can act undisturbed on the ventral wall of the chest. Added to this is a second important factor in the development of the systolic depression of the thoracic wall in adhesive pericardial disease, i. e., a change in the mechanics of the ventricular systole. Under normal conditions about five sixths of the decrease in volume is attained by longitudinal shortening of the ventricular cone, whereas the marginal movement contributes little to the expulsion of blood (Straub[7] and Schwarz[8]). When the pericardial cavity is obliterated, however, the longitudinal contraction of the heart is interfered with, for the pericardium is immovably attached by adhesions to the blood vessels at the base of the heart. In order to attain a sufficient stroke volume, this reduction in the longitudinal contraction is compensated for by increased marginal excursions. This agrees with the fact that in cases of distinct systolic depression of the thoracic wall roentgenologic examination often reveals remarkably large excursions of the ventricular margins.[9] This fact must be especially emphasized, for the generally accepted idea is that in cases of adhesive pericardial disease fluoroscopy reveals abnormally small movements of the ventricular margins exclusively. Exactly the reverse can, at least in many cases, be demonstrated. The great amplitude of the cardiac silhouette reminds one, at first glance, of that seen in cases in which there is a much increased stroke volume, as in marked bradycardia. Yet in obliterative pericardial disease the small amplitude along the arterial trunks is in vivid contrast to the large amplitudes of the ventricular margins. Hence, it may be concluded that the increased pulsation of the ventricle does not express

7. Straub, H.: Dynamik der Klappenfehler des linken Herzens, Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 41, 1929, p. 277; Die Dynamik des Herzens, in Bethe, A., and others: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, pt. 1, pp. 235 and 241.

8. Schwarz, G.: Ueber röntgenoskopische Messung und Analyse der Herzkammeraktion, Med. Klin. **16**:947, 1920.

9. Dr. H. Roesler gave me this information.

an increased ventricular stroke volume but corresponds to an altered mode of ventricular contraction. The increase in the marginal amplitude leads to an increased direct aspiratory action on the ventral wall of the chest, furnishing an explanation for the forceful systolic depression, which can be seen in certain cases of adhesive pericardial disease.

Frequently, when a patient with obliterative pericardial disease is being examined the systolic depression is much less noticeable than the abrupt diastolic propulsion of the thoracic wall at the beginning of diastole. This diastolic propulsion will generally be confused with the normal systolic heart beat if one neglects to palpate the radial pulse simultaneously so as to determine the cardiac phase.

Several factors are responsible for the appearance of the diastolic cardiac thrust. Skoda said he thought that this was merely a compensation for the systolic depression of the thoracic wall, but this cannot be fully accepted, since Brauer [10] has shown that the diastolic propulsion likewise may be observed after cardiolysis. Inhibition of the systolic change in the shape of the heart seems to be a decisive factor. Under normal conditions the systolic change in shape gives the heart, and thereby also the thoracic wall, a powerful thrust forward during systole, so that in the subsequent diastolic relaxation, an opposite (centripetal) movement of the heart and thoracic wall is called forth. Hence, the tendency to centrifugal movement caused by the diastolic filling of the ventricle cannot come into full play under normal conditions. But since in adhesive pericardial disease the systolic elevation of the heart is absent, the centrifugal impulse due to ventricular filling can act unrestrictedly on the thoracic wall. This is especially true in cases of congestive failure in which the blood is forced with increased momentum into the ventricles at the beginning of diastole.

Sahli said he believed that the diastolic cardiac thrust may be looked on as evidence for the presence of external adhesions, indicating that the thoracic wall is actively drawn inward from within; this would call forth the oppositely directed movement during diastole. Sahli stressed this point in view of cardiolysis, which he said he believed to be promising only if there are adhesions between the pericardium and the thoracic wall in addition to an obliteration. This opinion is erroneous in two ways: First, it makes no difference whether the heart causes a depression of the thoracic wall because of the presence of adhesions or because of an increased stroke volume, considerable contact of the enlarged heart with the thoracic wall or some other factor. In any case it has to do an increased amount of work, and the condition is relieved by resection of the adjacent stiff portions of the thoracic wall, as has been shown for the enlarged heart without pericardial adhesions by

10. Brauer, L.: Untersuchungen am Herzen, Verhandl. d. Kong. f. inn. Med. **21**:187, 1904.

French authors (Worms and d'Aubigné [11]). Also the previously mentioned observations at the bedside and at postmortem examination have shown that external adhesions are not necessary for the development of a diastolic cardiac thrust. In the aforementioned case of isolated obliteration of the pericardial cavity there was a typical diastolic forward thrust which for a long time imitated a normal cardiac thrust. Likewise, experiences with tricuspid regurgitation (Volhard [12] and Lang [13]), in which a diastolic cardiac thrust was reported in the absence of pericardial adhesions, made it clear that external pericardial adhesions are unnecessary for the development of these phenomena of pulsation.

Skoda has shown that the systolic depression of the thoracic wall in the presence of obliteration of the pericardial cavity is directed not perpendicularly to the frontal plane but toward the sternum. This movement is more marked in the area of the apical pole, while the intensity diminishes toward the sternum. This is explained by the fact that in the presence of pericardial obliteration the direct aspiratory effect of the heart on the thoracic wall prevails; this is more marked in the portion near the apex. The pulsatory depression on the left side calls forth an associated pulsatory movement on the right, where the ribs bulge slightly and move a little to the right. The summation of both pulsations leads to a frontal shift of the whole chest from left to right during systole.

A similar observation has been made in many cases of tricuspid regurgitation. With this valvular lesion the pulsation on the right side is an expression of a primary direct impulse caused by the impact of blood which has regurgitated into the liver. The hand placed on the thoracic wall perceives the forceful thrust. The pulsation on the right side in obliterative pericardial disease is an associated movement, much weaker than the one on the left and as a rule better perceived by inspection than by palpation. This is important in the differentiation of the two disease entities that are otherwise so similar. As a further point of differentiation it should be mentioned that with tricuspid regurgitation the systolic shift of the chest to the right is found to be much more distinct than the opposite movement during diastole, while in obliterative pericardial disease the diastolic propulsion is usually forceful and therefore represents a more impressive pulsatory phenomenon than does the systolic depression. Correspondingly, one finds

11. Worms, R., and d'Aubigné, R. M.: Une observation de thoracéctomie précordiale pour symphyse du péricarde, Bull. Soc. de pédiat. de Paris **26**:219, 1928.

12. Volhard, F.: Ueber Leberpulse und über die Compensation der Klappenfehler, Berl. klin. Wchnschr. **41**:522, 1904.

13. Lang, G.: Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, Deutsches Arch. f. klin. Med. **108**:35, 1912.

in constrictive pericardial disease that the pulsatory associated movement on the right side, consisting of a shift (diastolic) to the left, is abrupt and forceful, while the systolic propulsion on the right side is much weaker and takes place almost imperceptibly. The following report is of a patient who showed the characteristic pulsations in an impressive manner. The diagnosis of adhesive pericardial disease was proved by the roentgenologic demonstration of calcareous deposits.

B. F. was a man aged 19. A clinical diagnosis of adhesive pericardial disease was made, apparently on the basis of a tuberculous polyserositis, with moderate signs of heart failure. There was a definite bulge over the cardiac area. A diffuse pulsatory propulsion of the precordium was more marked in the fourth and fifth intercostal spaces, 2 fingerbreadths within the left midclavicular line. The first impression was of a systolic cardiac thrust. Comparison with the radial pulse showed that the propulsion took place during diastole, while there was a depression

Fig. 2 (patient B. F.).—The arrows indicate the direction of the pulsations of the thoracic wall.

of the ribs and soft tissues during systole. The diastolic movement was abrupt and marked—much more impressive than the systolic depression. The latter movement comprised nearly the whole left side of the ventral wall of the chest, evidently from the second rib to the costal arch. It was more marked between the left midclavicular and the parasternal line and affected ribs as well as soft tissues (fig. 1 *B*). The depression was not perpendicular to the frontal plane but was combined with a frontal movement directed to the right. The sagittal movement of depression prevailed over the lateral portions of the left side of the chest, while near the sternum the pulsatory component with frontal direction was more marked; the sternum itself revealed an almost pure frontal shift from left to right. The right side of the chest likewise showed a diffuse pulsation, extending from the second rib to the costal arch. As compared with that of the left side, the whole movement was much weaker, being best noted between the third and the fifth rib (fig. 1 *C*); here the movement of sagittal direction (systolic propulsion) was overlaid by a frontal shift to the right. The summation of the frontal pulsations of both sides of the chest gave a marked systolic shift of the whole

chest from left to right (fig. 2), but still more impressive was the jerky diastolic movement in the opposite direction. The pulsation at the right side over the hepatic area was much less pronounced than that in the upper portion of the chest. The liver extended 3 fingerbreadths beyond the costal arch in the right midclavicular line, and palpation revealed, in addition to a small presystolic wave, a large systolic elevation which was followed by marked diastolic collapse.

Percussion showed that the cardiac area extended 2 fingerbreadths beyond the right sternal border. The lower sternal area was flat. No abnormal dulness was found in the second and third intercostal spaces to the left of the sternum. Auscultation revealed that the first sound at the apex was moderately loud; there was reduplication of the second sound, the second part of which coincided exactly with the visible and palpable diastolic propulsion of the thoracic wall. A similar finding was noted over the base. Here the second sound was definitely split. Murmurs were not present. The rhythm was regular, and the heart rate was 88. The blood pressure was 100 systolic and 45 diastolic.

Roentgenograms showed that the cardiac silhouette was moderately enlarged to either side, the transverse diameter being 14.3 cm. There were unusually large pulsatory amplitudes along the left lower and apical borders; the latter showed a definite systolic elevation. The silhouette revealed a definite concentric movement of the cardiac borders during systole. The amplitudes along the silhouettes of the aorta and pulmonary artery were small, in contrast to the large amplitudes of the ventricular contours. Hence the marked marginal movements of the heart could not correspond to an increased stroke volume. In both oblique views calcareous deposits were noted along the surface of the silhouette.

Adhesive pericardial disease is differentiated from tricuspid regurgitation by the absence in the former of a forceful systolic hepatic regurgitation pulse. The combination of tricuspid regurgitation with adhesive pericardial disease makes the diagnosis of the latter condition extremely difficult. Since pulsatory phenomena on the left side of the chest not associated with a hepatic regurgitation pulse will be attributed first of all to tricuspid regurgitation, the detection of pericardial deposits of lime salt will be the only finding, in addition to tricuspid regurgitation, on which to base a diagnosis of adhesive pericardial disease.

SUMMARY

Diffuse pulsations of the thoracic wall in the presence of adhesive pericardial disease are by no means necessarily associated with external adhesions. Two factors play the main rôle: (1) an inhibition of the systolic change of shape of the heart whereby the aspiratory forces due to reduction of the ventricular volume during the systolic efflux prevail and (2) a change in the mechanism of volumetric diminution so that the marginal movements of the ventricles prevail because the longitudinal shortening of the ventricular cone is inhibited. Fluoroscopy in instances of obliterative pericardial disease associated with marked depression of the thoracic wall does not necessarily reveal a diminution of the marginal movements of the silhouette, as commonly accepted, but, on the contrary, rather strikingly large amplitudes may be observed.

The inhibited systolic change in the shape of the heart due to internal adhesions is of decisive importance for the appearance of a diastolic propulsion of the thoracic wall. External adhesions are not a prerequisite.

Similar to tricuspid regurgitation, adhesive pericardial disease is not rarely accompanied with a pulsatory movement of the whole chest directed from left to right during systole; this is due to a pulsatory associated movement of the right side of the chest. Tricuspid regurgitation is differentiated from adhesive pericardial disease by the absence in the latter of a forceful systolic hepatic regurgitation pulse.

PULSATIONS OF THE WALL OF THE CHEST

V. PULSATIONS ASSOCIATED WITH MITRAL REGURGITATION AND ANEURYSMAL DILATATION OF THE LEFT AURICLE

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Under normal conditions one may not expect the left auricle to transmit its movements against the thoracic wall, because it lies almost exclusively at the dorsal aspect of the heart. Also, the degree of the pulsatory amplitude is much too weak to produce visible or palpable pulsatory phenomena. In the presence of disease of the mitral valve the left auricle may dilate exclusively dorsad and occasionally to the right side of the chest (Stoerk [1]). An anterior roentgenogram will reveal that the left auricle overlaps the right auricle on the right side, resulting in a subdivision of the right cardiac contour. In the presence of mitral regurgitation of a higher degree one notices that these two arches show pulsations in opposite directions. The upper arch corresponds to the left auricle and shows a forceful lateral movement during systole, while the lower arch (right auricle) simultaneously reveals a smaller movement inward. Mahaim [2] was the first to describe this seesaw movement, and Roesler [3] interpreted it correctly when he ascribed the movement of the upper arch to the impact of the regurgitating blood and the pulsations of the caudal arch as transmitted from the contracting right ventricle.

As the large left auricle bulges to the right, it may in certain cases transmit its pulsations against the ventral wall of the chest, giving rise to a systolic pulsatory propulsion which, even without the aid of a roentgenographic study, may permit one to diagnose the underlying condition. This protrusion of the thoracic wall is noted beyond the right sternal border. It may be differentiated from other pulsations along the parasternal portions of the ribs, as encountered in disease of the mitral valve, in that it causes a shock against the thoracic wall

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Translated by Hugo Roesler, M.D., Philadelphia.

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors.

1. Stoerk, O.: Zur Topographie des Mediastinum bei normaler und bei pathologischer Herzform, Ztschr. f. klin. Med. **69**:32, 1910.

2. Mahaim, I.: Un symptôme radiologique de l'anévrisme de l'oreillette gauche, Schweiz. med. Wchnschr. **57**:183, 1927.

3. Roesler, H.: Rechtsseitige, mitgeteilte Hiluspulsation bei aneurysmatischer Erweiterung des linken Vorhofes, Fortschr. a. d. Geb. d. Röntgenstrahlen **40**:1017, 1929.

in a large area, extending between the second and the sixth rib to the right midclavicular line. Such a widespread heaving of the right wall of the chest cannot be interpreted as a simple associated movement, as it may accompany the action of a hypertrophied right ventricle. Percussion reveals in association with it an extension of the cardiac dulness far to the right. The content of such an aneurysmatically enlarged right auricle may be up to 2 liters, and the rest of the heart, though not small, looks like an appendix to the left auricle. The left auricle embraces the right auricle from behind and may extend beyond it for more than a handbreadth when visualized from in front.

Roentgenograms show it as a big bulge silhouetted at the right border with its convexity directed to the right and upward (Lutembacher [4]). The left auricle may form the whole right cardiac border, and within one notices the lateral contour of the denser shadow of the right auricle. The posterior (lower) lobe of the right lung becomes atelectatic and is displaced on the right and upward; the left auricle is found in broad contact with the ventral wall of the chest and the diaphragm, forming a depression on the latter (Goedel [5]). The forceful regurgitation of blood in cases of mitral regurgitation may thus create a pulsation of larger portions of the right side of the chest. These pulsations may be demonstrable as far as the right axilla and occasionally cause a jerky movement of the whole chest, directed to the right during systole.

Bedford [6] described such pulsations in association with an aneurysmatically dilated left auricle in two cases, and my colleagues and I have observed it in eight instances.[7] In all these cases high grade mitral regurgitation was present. The following case serves as a typical example.

P. A. was a woman aged 26. In this case the clinical diagnosis was mitral stenosis and regurgitation with auricular fibrillation. The patient was digitalized and showed no definite signs of cardiac failure. Examination revealed immediately a widespread forceful pulsatory movement on the right side of the chest (fig. 1). The center of pulsation, where the systolic propulsion of ribs and soft tissue was most marked, was in the right midclavicular line between the fourth and the fifth intercostal space. Associated with it was a definite movement directed to

4. Lutembacher, R.: Anévrisme de l'oreillette gauche, Arch. d. mal. du cœur **10**:145, 1917; Deux nouveaux cas d'anévrisme de l'oreillette gauche, ibid. **11**:434, 1918.

5. Goedel, A.: Eine ungewöhnliche Form der Herzvergrösserung (enorme Vorhofvergrösserung) bei Mitralstenose, Wien. klin. Wchnschr. **42**:427 (April 4) 1929.

6. Bedford, D. E.: Two Cases of Aneurysmal Dilatation of the Left Auricle, Proc. Roy. Soc. Med. **20**:328, 1927.

7. Dressler, W.: Die Brustwandpulsationen als Symptome von Herz- und Gefässkrankheiten, Vienna, Wilhelm Maudrich, 1933.

the right and upward. The pulsation affected almost the whole right side of the chest and extended cephalad as far as the second rib and caudad to the costal arch. Its intensity was diminished in the region below the sixth rib, i. e., in the hepatic area. A definite systolic shock was palpated in the right axilla (fig. 1 *B*). The pulsation on the right actually governed the movement of the whole chest, which showed an abrupt jerky systolic shift to the right and cephalad. This movement was palpated over the right shoulder, and it could even be noticed through a blanket. The sternum and a small area along its left border, extending from the third rib to the costal arch, participated in this pulsatory propulsion of the right side of the chest. The rest of the whole left side of the chest revealed a definite systolic depression which affected soft tissues as well as ribs. This movement was more marked in the lateral and caudal aspects below the sixth rib and was combined with the movement to the right. With the exception of the aforementioned small medial area, the whole left side of the chest appeared to be forcefully "drawn in" during systole. This movement was apparently caused by the pull of the systolic bulge on the right. In addition, an aspiratory effect, caused by the bulging right wall of the chest as well as by the full emptying of the left ventricle (mitral regurgitation), undoubtedly played an important rôle. This explains why the area of depression extended to the back, where there was

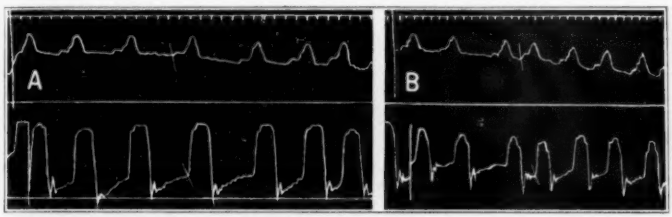

Fig. 1 (patient P. A.).—The graph demonstrates the systolic propulsion of the right side of the chest caused by the pulsating left auricle. The lower graph is for the apical thrust. The upper graph is for the (*A*) third intercostal space, 4 cm. outside the right midclavicular line, and (*B*) for the fourth intercostal space in the right anterior axillary line.

a definite systolic depression of the soft tissues and ribs over the left caudal aspect, lateral to the scapular line (Broadbent's sign). The development of these unusually forceful pulsations was obviously enhanced by the flexible skeleton of the young slender patient. The apical thrust was easily felt as a forceful elevation, but it was poorly visible within the diffuse depression on the left side; it was located in the sixth intercostal space, 2 fingerbreadths beyond the left midclavicular line, and was definitely widened and of increased resistance.

Percussion revealed that the cardiac dulness extended 4 fingerbreadths beyond the right sternal border in the fourth intercostal space. There was absolute flatness over the sternum, extending from Louis' angle to the ensiform process. To the left of the left sternal border was an area of dulness that was 2 fingerbreadths wide in the second intercostal space and 4 fingerbreadths wide in the third intercostal space.

Auscultation revealed over the apex a long, loud, blowing systolic and a short, booming diastolic murmur. The latter was accompanied with a palpable diastolic thrill. The systolic murmur was heard over the whole cardiac area, though with

less intensity. The pulmonic second sound was moderately increased. The action of the heart was irregular, auricular fibrillation being noted in the electrocardiogram. The heart rate was 84. The blood pressure was 115 systolic and 55 diastolic. The liver extended for 3 fingerbreadths below the costal arch in the right midclavicular line; it revealed a weak systolic pulsation. The same findings were present over the veins of the neck. Cyanosis and edema were not noted.

Roentgenograms showed an enlarged silhouette of mitral configuration, with a transverse diameter of 20 cm. (fig. 2). The lateral wall of the chest was reached on the left side and was approached on the right side. The left auricle was enormously enlarged, forming the whole right contour of the heart, and was the cause of the extensive dilatation to the right. It rested directly on the diaphragm. Within the cardiac shadow was a denser nuclear shadow, which corresponded to the right auricle. The dome of the left auricle projected toward the right axilla at the level of the fourth intercostal space. The right auricle was dilated likewise and was embedded within the left auricle.

Several facts prove that the pulsations of the right wall of the chest were caused by the regurgitation of blood into the aneurysmatically enlarged left

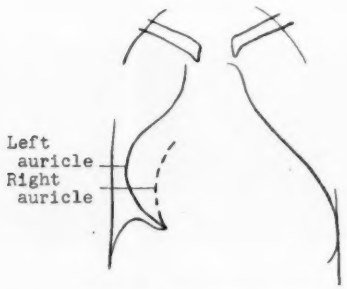

Fig. 2.—An orthodiagram, showing the large silhouette with the mitral configuration. The new right cardiac border was formed by the aneurysmatically enlarged left auricle. The original right cardiac border, as formed by the right auricle, is seen within (dash line).

auricle: First, this phenomenon could be observed only in those cases in which high grade mitral regurgitation was present; second, because fluoroscopic observation revealed a forceful lateral systolic pulsation of the contour of the left auricle, corresponding to the direction of the regurgitating blood; third, because fluoroscopic observation revealed in every instance that the maximum pulsation of the thoracic wall coincided with the convexity of the contour of the left auricle.

Such a pulsation of the aneurysmatically dilated left auricle is remarkably often associated with a ventricular venous pulse in the veins of the neck and in the liver. It seems improbable that this finding should always be attributed to associated tricuspid regurgitation, particularly because of the unusually good compensation, which may last for years. It is conceivable that the left auricle, which is in close con-

tact with the right auricle and embraces it from behind and pushes it ventrad, imparts to it its forceful systolic pulse which then will be transmitted to the veins. It must be recalled also that the left auricle, by displacing the lung, comes into direct contact with the diaphragm and thus may directly transmit its pulsations to the liver.

Pulsations of the thoracic wall which are caused by the left auricle may be recognized without difficulty even in the presence of tricuspid regurgitation. The auricular pulsations show their maximum strength above the lung-liver border, approximately at the level of the fourth intercostal space, while pulsations of the thoracic wall transmitted from the pulsating liver are, of course, best felt over the caudal third of the chest.

SUMMARY

A pulsating propulsion of the right wall of the chest is observed in cases of aneurysmal dilatation of the left auricle to the right. Mitral regurgitation is a prerequisite, and the pulsations are caused by the impact of the blood regurgitating into the left auricle. The maximum of these pulsations as a rule is found in the right midclavicular line between the fourth and the sixth rib, and pulsations may be observed as far as the right axilla.

OPTIC NEURITIS IN HYPERTHYROIDISM

REPORT OF A CASE WITH REVIEW OF THE LITERATURE

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AND

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PHILADELPHIA

Edematous and inflammatory diseases of the optic nerves are not always manifestations of a local lesion. In fact, it is known that these nerves, although well protected from direct injury, are often involved by disease processes that are far removed from the eyeball itself. Disease of the optic nerves may be the first indication of extracranial disease. From a review of the literature on the etiology of optic neuritis table 1 has been prepared (Fuchs [1]). It may not be entirely complete, but it serves to illustrate the many diverse conditions that have been reported as affecting the optic nerves.

It is obvious from the multiplicity of the reported causes of optic neuritis that in a given case it is difficult to settle on any one etiologic factor to the satisfactory exclusion of all others. In spite of this, we feel justified in reporting a case of optic neuritis as illustrative of one of the rarer causes of this condition, namely, hyperthyroidism.

REPORT OF CASE

L. L., a woman aged 30, was admitted to the service for patients with thyroid disease of the late Dr. Charles H. Frazier at the Hospital of the University of Pennsylvania on March 29, 1936, complaining of "swelling of the neck" and insomnia. The patient had apparently been in good health until February 8, less than two months before admission to the hospital, when she had an attack of "intestinal grip." The symptoms at this time consisted of general malaise, vomiting, fever, loss of appetite and weakness. The patient remained in bed for two weeks. The temperature slowly subsided, but the malaise and weakness continued. A physician was called, and the swelling in the neck was noted for the first time. Then insomnia, nervousness and tremors began to develop. The patient lost 22 pounds (10 Kg.), the weight being reduced from 110 to 88 pounds (50 to 40 Kg.), a loss of 20 per cent of the total body weight, within the period of illness preceding her admission to the hospital. She had had no visual distur-

From the Department of Surgery, the Hospital of the University of Pennsylvania.

1. Fuchs, E.: Disease of the Eye, ed. 15, revised by M. Salzman and translated by E. V. L. Brown, Philadelphia, J. B. Lippincott Company, 1935, pp. 395-398.

bances. She had experienced some dyspnea on exertion since the onset of the "grip," and she believed that she had had some edema of the ankles evenings during the week preceding her entrance into the hospital. She had been bothered by a dry, nonproductive cough. The expected menstrual period in February had not occurred, and she had not menstruated since. The past, family and social histories contained no pertinent facts.

Physical Examination.—The pulse rate was 140 per minute, the respiratory rate 28 per minute and the temperature 98 F. The blood pressure was 140 systolic and 80 diastolic. The patient was nervous and apprehensive. There were generalized tremors of the body. Examination of the fundi revealed optic neuritis. The details of this and subsequent examinations of the eyegrounds and visual acuity are given in table 2. There were lateral nystagmoid movements on extreme lateral gaze in both directions. Except for a suggestion of exophthalmos on both sides, there was no external ocular sign of thyrotoxicosis. The nasal septum was slightly deviated. The oral cavity presented dental sepsis and chronically infected

TABLE 1.—*Etiologic Factors Reported in Disturbance of the Optic Nerve*

I.	Diseases of the central nervous system
	1. Lesions producing increased intracranial pressure: brain tumor, brain abscess, hydrocephalus, etc.
	2. Infections: syphilis, tuberculosis, encephalitis, meningitis and poliomyelitis
	3. Multiple sclerosis, syringomyelia and Schilder's disease
II.	Generalized infections: acute exanthemas, diphtheria, pertussis, mumps, pneumonia, grip, influenza, Malta fever, Weil's disease, malaria, typhus fever, tularemia, frambesia, etc.
III.	Other general systemic diseases: diabetes, nephritis, hypertension, etc.
IV.	Blood dyscrasias: anemias, leukemias and purpura haemorrhagica
V.	Focal infections: infections of teeth, tonsils and adenoids; sinusitis; mastoiditis and parotitis
VI.	Exogenous toxins: lead, alcohol, iodoform, arsenic, carbon disulfide, thallium, apiol, nicotine, tryparsamide, acetarsone, naphthalene and a host of others
VII.	Orbital conditions: tumor, infection, trauma, etc.
VIII.	Endocrine disturbances: hyperthyroidism, hypothyroidism, pituitary disease, etc.
IX.	Gynecologic phenomena: pregnancy, lactation, eclampsia, puberty, menstrual disturbances and menopause
X.	Miscellaneous: vitamin deficiency, antirabic inoculations, protein therapy, heredity, helminths and "cryptogenic" forms

tonsils. A mucopurulent postnasal drip was noted in the oropharynx. The thyroid gland was moderately and diffusely enlarged. Percussion of the area over the heart revealed slight cardiac enlargement, and a systolic murmur was heard over the pulmonic area. The deep reflexes were generally hyperactive. Abortive ankle and patellar clonus, with a suggestion of a bilateral Babinski sign but none of its confirmatory signs, comprised the neurologic findings.

Laboratory Examination.—The basal metabolic rate on the day following the patient's admission to the hospital was plus 82 per cent. All subsequent values for the metabolic studies and their relationship to the weight, pulse rate and course of the disease are presented in table 3.

An intravenous phenolsulfonphthalein test showed 30 per cent excretion of the dye in fifteen minutes, 30 per cent in the next forty-five minutes and fifteen per cent at the end of two hours, giving a total excretion of dye of 75 per cent. The urea nitrogen content of the blood was 9 mg. per hundred cubic centimeters. The urea clearance was 52 per cent of the average normal function. Details of the more complete urinary studies are recorded in table 4.

Roentgenographic study of the head revealed enlargement of the pituitary fossa and equivocal evidence of increased intracranial pressure.

Gastric analysis with histamine showed achlorhydria.

The pressure of the cerebrospinal fluid varied from 80 to 100 mm. of water. The protein content of the fluid was 1.25 units (normal). One lymphocyte and 2 erythrocytes were noted per cubic millimeter of cerebrospinal fluid. The Wassermann test of the fluid gave a negative reaction, and the colloidal gold readings were 0000000000.

TABLE 2.—*Eyegrounds and Visual Acuity*

Date, 1936	Retina			Acuity*	
	Vessels	Hemorrhages	Exudates	Disks	Right	Left
4/ 1	Arteries contracted and tortuous; veins engorged	Fresh; few flame-shaped; bilateral	None	Margins fluffy; normal color; good vascularity; swelling, 1 diopter on left; 2 diopters on right		
4/ 2	.....	.....	.....	.....	6/30	6/60
4/ 9	.....	.....	.....	.....	6/12 —2 s.c.	6/15 s.c.
4/13	Arteries normal; veins slightly engorged	None on left; few right	None	Unchanged; bilateral swelling of 2 diopters		
4/17	.....	.....	.....	.....	6/12 —2 c.c.	6/12 —1 c.c.
4/23	Normal	None	None	Swelling of 1 diopter on left; 1 diopter on right	6/ 9 —1	6/12 —3
6/ 2	Normal	None	None	Margins of disks still fuzzy; bilateral swelling of 1 diopter	6/12 —1 c.c.	6/12 —2 c.c.
6/12	.....	.....	.....	.....	6/12 —2 c.c.	6/ 9 —3 c.c.
6/19	.....	.....	.....	.....	6/12 —3 c.c.	6/12 —3 c.c.
10/27	.....	.....	.....	.....	6/15 —1 c.c.	6/12 —1 c.c.
10/28	Vessels moderately full and tortuous	None	None	Margins faintly hazy; no swelling; color normal		

* s.c. indicates without correction, and c.c., with correction.

TABLE 3.—*Basal Metabolic Rate, Pulse Rate and Weight Throughout the Treatment*

Date, 1936	Basal Metabolic Rate, Plus %	Weight, Pounds	Pulse Rate per Minute
3/30	82	87	120
4/ 4	44	81	100
4/ 7	36	80	96
4/11	33	79	102
4/14	31	83	116
Operation, right lobectomy			
4/24	28	81	92
6/ 2	56	102	126
6/ 5	49	101	124
6/ 9	41	103	122
Operation, left lobectomy			
6/19	31	102	92
9/23	1	112	100

The protein content of the blood serum was 4.7 per cent, and the chloride content was 103.4 milliequivalents per liter. The blood count on the day following the patient's admission to the hospital showed: erythrocytes, 4,300,000; leukocytes, 7,600, and hemoglobin (Sahli), 72 per cent. The Wassermann reaction of the blood was negative.

Course.—On April 2 the patient was started on sedation, iodine therapy, enforced rest in bed and a high caloric diet. She reacted well to the treatment and showed such definite clinical improvement that subtotal thyroid lobectomy on the right was performed by Dr. Julian Johnson on April 18. The postoperative course was not unusual. The wound healed by primary intention, and the patient was discharged on April 24, with a basal metabolic rate of plus 28 per cent. She was to receive iodine therapy regularly and was instructed to return in six weeks for the second stage of the operation.

After discharge the patient steadily improved until the last week in May. She then began to notice increasing nervousness and palpitation. She was readmitted to the hospital on June 6. The pulse rate was 120 per minute. The blood pressure was 140 systolic and 80 diastolic. The patient weighed 104¼ pounds (47.5 Kg.). The left lobe of the thyroid gland was found to be diffusely enlarged. The heart was normal in size. A blood count revealed 4,400,000 erythrocytes, 7,800 leukocytes and a hemoglobin value of 88 per cent. The basal metabolic rate was plus

TABLE 4.—*Renal Studies; Twenty-Four Hour Concentration Test*

	Normal Figures	Examinations		
		4/17	6/7	10/27
Specific gravity	1.025 or more	1.021	1.028	1.032
Amount of urine, cc.	380 average	407	546	146
Casts, thousands	5 or less	291	79	67.5
Red blood cells, thousands	500 or less	1,000	1,200	600
Epithelial cells and leukocytes, millions	2 or less	7.3	2.1	0.5
Blood urea nitrogen after restriction of fluids, mg. per 100 cc.	Up to 21	21.1	21.7	16.7
Urea clearance, %	55 to 100	52	72	60
Protein in urine, Gm. in 12 hours	0.1 or less	0.55	0.3	0.6
Plasma protein, Gm. per 100 cc.	6 to 7	6.56	.....	6.48

56 per cent. A roentgenogram of the sinuses showed the right antrum to be clouded, but an otolaryngologist said he considered that the sinuses presented no clinical evidence of active disease. The patient was again treated with rest, sedation, iodine and a high caloric diet. The basal metabolic rate finally dropped to plus 41 per cent. On June 13 lobectomy on the left was performed by Dr. Robert Brown. The immediate postoperative course was stormy, but the patient recovered and was discharged with a basal metabolic rate of 31 per cent on June 20.

Subsequently the patient was followed in the section for patients with endocrine disorders of the outpatient department of the University Hospital. When last seen, in October 1936, she did not present any clinical signs and had no symptoms of thyrotoxicosis. Although the pulse rate was still a bit hurried, the basal metabolic rate was plus 1 per cent. The details of the results of studies of the kidneys, fundi, visual acuity and visual fields are given in the accompanying tables and charts.

REVIEW OF THE LITERATURE

According to the number of cases of disturbance of the optic nerves associated with hyperthyroidism that have been recorded in the litera-

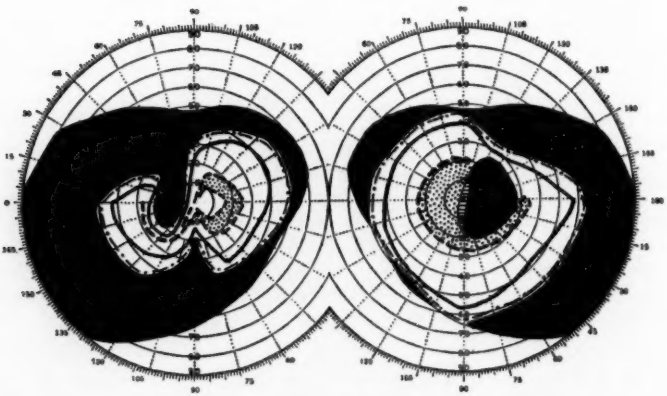

Chart 1.—These visual fields were taken before treatment with iodine was begun. Note the tendency toward bitemporal heteronymous hemianopia and the enlargement of the blindspots. In charts 1 to 8 the solid line indicates the field of vision as shown by a 1 degree white test object; the dash and dot line, that shown by a 2 degree white test object; the dash line, that shown by a 1 degree red test object, and the dotted line, that shown by a ½ degree red test object. The blackened area indicates absolute scotoma; the horizontally shaded area, scotoma for a 1 degree white test object; the vertically shaded area, that for a 1 degree red test object, and the dotted area, doubtful scotoma for a 1 degree red test object.

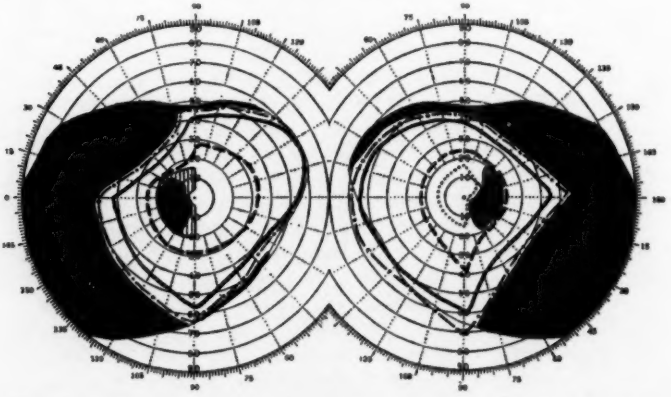

Chart 2.—These fields were obtained after one week of treatment. Note the marked improvement.

ture, the condition must be rare. In 1921 H. Sattler [2] and Behr [3] published excellent reviews of this subject. Sattler reported the case of a 52 year old man who suffered from exophthalmic goiter for eight years before thyroidectomy was performed. He had blurring of vision and slight pallor of the temporal half of each optic nerve head, with considerable reduction in the visual acuity. There was marked improvement of the disturbance of the optic nerves (retrobulbar neuritis), with recession of the symptoms of hyperthyroidism after thyroidectomy. Sattler collected from the literature reports of thirteen other cases of disease of the optic nerve due to thyrotoxicosis. Behr reported four causes of Dercum's disease with changes in the optic nerves. He then discussed the production of optic neuritis by certain endogenous toxins, particularly in hyperactivity of the thyroid gland. He added reports of four further cases cited in the literature.

In addition to these cases we have found that von Hippel [4] recorded four cases of changes in the optic nerves associated with hyperplasia of the thyroid gland. However, he reported no basal metabolic determinations in any of these cases, and a study of his protocols leads one to believe that these were not cases of true hyperthyroidism. Keogh [5] reported a case of exophthalmic goiter in which the immediate postoperative period there developed partial blindness associated with atrophy of both optic nerves. He suggested that this was due to some undetermined form of intestinal toxemia associated with hyperthyroidism.

Since the publication of the aforementioned reviews few cases of optic neuritis caused by hyperthyroid disease have been reported in the literature. In his textbook on the eye Moore [6] stated that he had noted one case of retrobulbar neuritis associated with exophthalmic goiter. More recently, this author,[7] in discussing ocular diseases in exophthalmic

2. Sattler, H.: Ueber einen Fall von Neuritis nervi optici retrobulbaris als Frühsymptom der Basedowschen Krankheit, Wien. med. Wchnschr. **71**:1084-1088, 1921.

3. Behr, C.: Sehnervenentzündungen bei Störungen der inneren Sekretion im Verlauf der Adipositas dolorosa (Dercumschen Krankheit), Deutsche. Ztschr. f. Nervenh. **71**:275-296, 1921.

4. von Hippel, E.: Toxische Sehnervenerkrankung mit seltener Aetiologie, in von Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1923, vol. 7 B, pt. 2, pp. 401-405; Das Abderhaldensche Dialysierverfahren beim Glaukom sowie bei einigen Sehnervenerkrankungen, Arch. f. Ophth. **90**:198-245, 1915.

5. Keogh, C. H.: Graves' Disease: A Case with Post-Operative Amblyopia, New York M. J. **104**:457, 1916.

6. Moore, R. Foster: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Co., 1925, pp. 219-220.

7. Moore, R. Foster, in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 817.

goiter, stated that these symptoms are "limited to the adnexa of the eyeball" and that "no pupillary or fundus changes occur." Wiener [8] mentioned under unusual ocular complications of goiter atrophy of the optic nerve and neuroretinitis. Naffziger and Jones [9] in a report of six

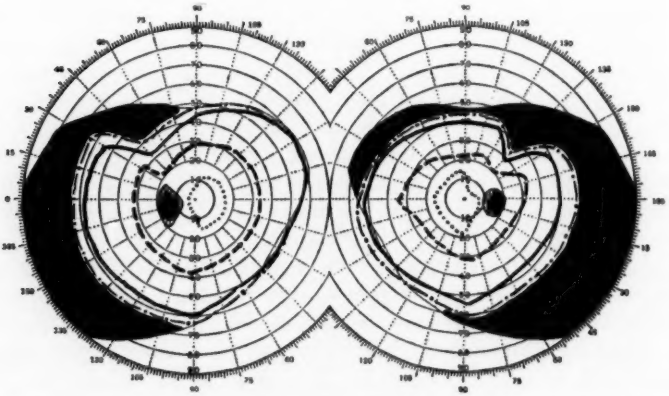

Chart 3.—These fields were taken the day before the first stage of thyroid lobectomy. There has been remarkable improvement still with a tendency to defects in the upper quadrants.

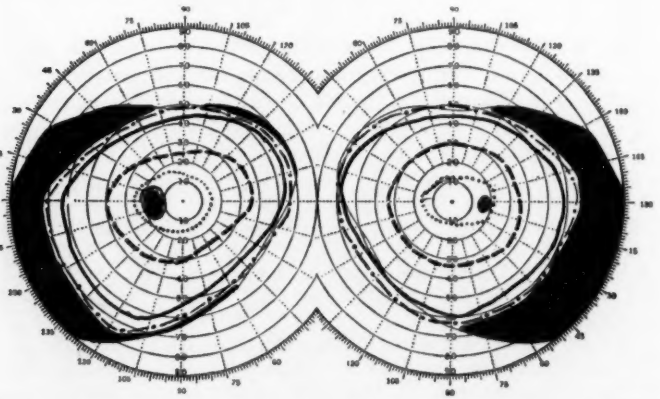

Chart 4.—Five days after the first stage of the operation. The blindspots are now nearly normal in size, and the quadrantic defect is no longer present.

8. Wiener, M.: Diseases of the Eye, J. Missouri M. A. **23**:211-212, 1926.

9. Naffziger, H. C., and Jones, O. W., Jr.: Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99**:638-642 (Aug. 20) 1932.

cases of progressive exophthalmos following thyroidectomy noted swelling and atrophy of the optic disks in five cases. In addition Friedenwald [10] reported a case of choked disk associated with a similar type of exophthalmos. However, Bothman [11] had pointed out that distur-

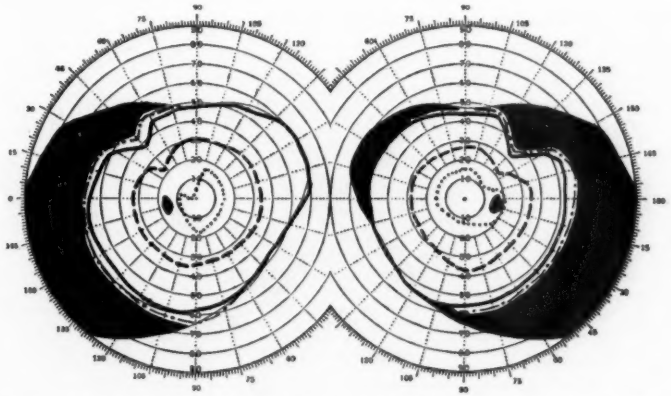

Chart 5.—After six weeks the visual fields have regressed, along with the return of thyrotoxic symptoms. Again hemianopia is suggested, and the defect in the upper outer quadrant is present.

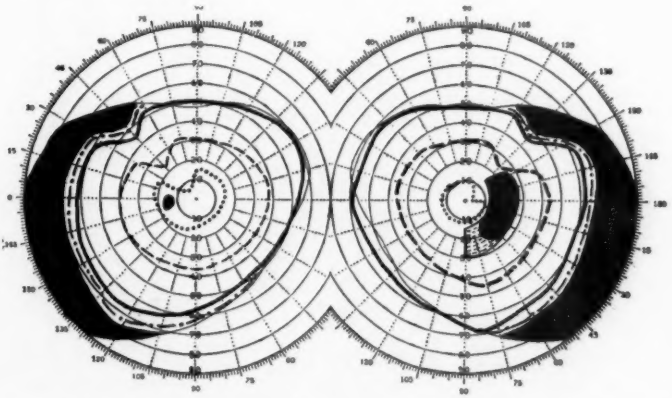

Chart 6.—Ten days after further treatment in the hospital improvement is again noted. The blindspot in the left eye is definitely enlarged.

10. Friedenwald, J. S.: Orbital Myositis and Choked Disk in Exophthalmic Goitre, Ann. Surg. **96**:995-997, 1932.

11. Bothman, L.: Endocrines in Ophthalmology, Illinois M. J. **65**:226-235, 1934.

bances of the optic nerves are not infrequently seen when the eyeball protrudes 25 mm. or more, and it is likely that the changes in the optic nerves associated with this type of exophthalmos are mechanical in origin, as suggested by Naffziger.[12] In a study of the ocular signs in

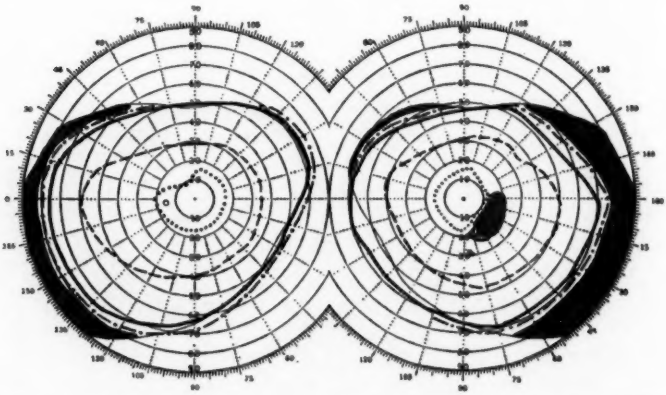

Chart 7.—These visual fields were obtained about six days after the second thyroid lobectomy had been performed.

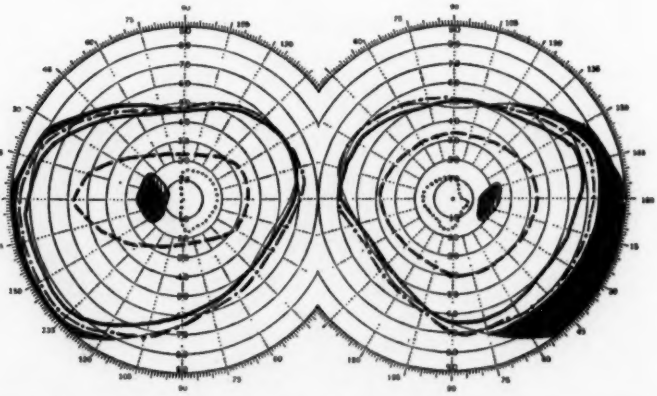

Chart 8.—These fields were obtained four months after the final operation. There are no signs or symptoms of hyperthyroidism. The basal metabolic rate was plus 1 per cent.

12. Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, with Special Reference to Alterations in the Extra-Ocular Muscles and the Optic Disks, Arch. Ophth. **9**:1-12 (Jan.) 1933.

one hundred unselected cases of hyperthyroidism Holloway, Fry and Wentworth [13] noted "no atrophy, optic neuritis or choking of the discs."

Observations on thyroid feeding, both in human beings and in experimental animals, lend further support to the concept of the etiologic relationship between hyperthyroidism and changes in the optic nerves. Coppez [14] reported on five patients with obesity who had been taking large doses of thyroid over long periods. Visual disturbances developed resembling those of tobacco amblyopia with central scotomas. The visual acuity was reduced to less than 10 per cent of normal. After stopping the medication all of these patients recovered. Aalbertsberg [15] treated a myxedematous patient with dried thyroid gland, and the patient subsequently lost the vision in both eyes. Ophthalmologic examination revealed hyperemia of the disks. After cessation of the thyroid medication the vision in the right eye improved, while atrophy of the left optic nerve developed. Standish [16] has reported optic neuritis in patients who were taking thyroid for obesity. Birch-Hirschfeld and Inouye [17] fed increasing doses of thyroid substance to a number of dogs. In one of the animals pallor of the optic disks developed, with contraction of the retinal arteries. Histologic examination showed degeneration of the fibers of the optic nerves and destruction of the ganglion cells of the retinas.

COMMENT

Several interesting questions arise from a study of our case. First, was the thyrotoxic state the only active agent in the production of the optic neuritis? In order to prove this it would be necessary to establish the absence of an etiologic relationship of (1) the foci of infection in the teeth and tonsils and possibly that in the sinuses, (2) the renal disturbance and (3) the initial attack of "intestinal grip." All of these conditions have been reported as causes of inflammation of the optic nerve.

We have already stated that the complete and satisfactory exclusion of all but one etiologic factor in a given case of this type is difficult. However, there are certain considerations in this particular case which point to thyrotoxicosis as the chief, if not the sole, causative agent.

13. Holloway, T. B.; Fry, W. E., and Wentworth, H. A.: Ocular Signs in One Hundred Unselected Cases of Goitre, J. A. M. A. **92**:35-41 (June 5) 1929.

14. Coppez, H.: Névrite optique par absorption de thyroïdine, Arch. d'opht. **20**:656-662, 1900.

15. Aalbertsberg, G.: Neuritis optica door het gebruik van schildklier, Nederl. tijdschr. v. geneesk. **2**:1125, 1902.

16. Standish, cited by Bothman.[11]

17. Birch-Hirschfeld, A., and Inouye, N.: Experimentelle Untersuchungen über die Pathogenese der Thyreodinamblyopie, Arch. f. Ophth. **61**:499-523, 1905.

An obvious but nevertheless convincing argument presents itself to minimize the possibility of any relationship between the foci of infection and the optic neuritis. The dental, tonsillar and sinus conditions have remained untreated and unchanged; the disease of the optic nerves has greatly improved.

The occurrence of disease of the optic nerves in renal dysfunction is, of course, well known. It is usually associated with uremia and hypertension. In the present case there was no history suggestive of nephritis. The slight elevation of the blood pressure with a wide pulse pressure was of the type frequently seen in thyrotoxicosis rather than that of renal disease. The special studies which revealed mild renal impairment were requested for the sake of completeness in studying this case. The clinical picture itself had not suggested them. It seems unlikely that changes in the eyegrounds of this nature and degree could be caused by the mild renal impairment present in this case. There was a slight change in the direction of improvement in the renal condition during the period of study.

Renal changes which in themselves were secondary to or at least associated with thyroid disease have been reported. Graupner [18] found in two patients with severe hyperthyroidism who died in delirium shortly after operation degenerative changes in the renal epithelium, progressing even to necrosis in one case. Von Monakow [19] described a case of hyperthyroidism with marked albuminuria and edema combined with poor elimination of chloride. Von Müller [20] reported the case of a 62 year old woman with definite goiter associated with secondary parenchymatous renal degeneration, as evidenced by a low concentrating power and high blood pressure (210 mm. of mercury) with cardiac hypertrophy, persistent albuminuria, edema and pseudochylous ascites. However, establishment of an etiologic relationship between the hyperthyroidism and the renal impairment in this case is not an object of discussion. The possibility of such a relationship has merely been suggested.

As far as the etiologic significance of "intestinal grip" is concerned, we wish to point out the all too frequent inclusive nature of such a diagnosis. From the description of the patient's symptoms and from the continuity of the symptomatology with that of the thyroid over-

18. Graupner: Nierenkrankung bei Basedowscher Krankheit, München. med. Wchnschr. **57**:1695, 1910.

19. von Monakow, P.: Beiträge zur Kenntnis der Nephropathien, Deutsches Arch. f. klin. Med. **115**:224, 1914.

20. von Müller, F.: Veröffentl. a. d. Geb. d. Mill-Saw.-Wes. **65**:33, 1917; cited by von Volhard, F.: Nieren und ableitende Harnmege, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, p. 1052.

activity, one wonders if this was not really the acute onset of the thyrotoxic state and not a grippal infection.

A study of the changes in the visual fields in relation to the fluctuation in the hyperthyroid state supplies the most convincing evidence in establishing thyrotoxicosis as the chief etiologic agent. First, the effect of preoperative iodine therapy is to be noted by comparing charts 2 and 3 with chart 1. The continued improvement after excision of the right lobe is shown in chart 4. During the period between the first and second stages of the operation the hyperthyroidism again increased, as indicated by the clinical picture and the basal metabolic rate. Concomitant with this was regression of the visual fields, as shown in chart 5. After the final lobectomy the visual fields improved more definitely and more completely than ever before (charts 7 and 8).

Another interesting question that arises in this case is that of the actual mechanism of the production of the changes in the optic nerves. Many authors believe this is due to a toxin produced by the thyroid gland, an endogenous toxin. In some cases, but certainly not in this one, the exophthalmos with retro-orbital pressure on the optic nerves is undoubtedly the etiologic factor. It may be that hyperthyroidism, a disease well known for its effect on the nervous system, sensitizes the optic nerve to the damaging influence of mild infections, renal disturbances and other disorders which alone would be harmless.

The type of disturbance of the visual fields, the suggested bitemporal heteronymous hemianopia and later the defects in the upper outer quadrants suggest chiasmal pressure from a swollen pituitary body. The edema of the optic nerve heads less readily yields to such an explanation. That there may be hypertrophy and hyperactivity of the pituitary gland with thyroid disease is possible. The increase in size of the pituitary fossa lends weight to this theory.

CONCLUSIONS AND SUMMARY

A case of thyrotoxicosis is presented in which optic neuritis was found to be an associated condition.

Despite the presence of other possible etiologic factors, because of the parallel fluctuations of the inflammation of the optic nerves and the thyrotoxic state, it is believed that hyperthyroidism was the chief cause of the optic neuritis.

It is pointed out that this condition must be rare and that the mechanism of the relationship is not definitely known.

The studies of the visual fields were made by Dr. Hazel Wentworth; the studies of the eyegrounds, by Drs. William Pettit and Wilfred Fry, and the special renal studies, by Dr. Eugene Landis.

GASTRIC ACID DURING RECURRENCES AND REMISSIONS OF DUODENAL ULCER

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The control of gastric acidity is still considered the major objective of therapy by many gastro-enterologists who believe hypersecretion to be the most important etiologic factor in the genesis of ulcer. This concept is maintained despite the accepted fact that there exists a marked variation in acidity not only in the ulcer-bearing patient but also in the normal healthy person. We do not concur with the belief that there is any exact relationship between the degree of gastric acidity and the symptomatology or behavior of an ulcer.

Although the preponderance of clinical and experimental evidence definitely opposes the correlation of gastric acidity with the production either of gastric pain or of the ulcer itself, the majority of clinicians employ and teach the precepts of neutralization therapy. Some investigators are still ascribing etiologic and therapeutic significance to deviations from the so-called normal levels of gastric acidity in patients with ulcer. In an excellent review of the subject of the mechanisms of pain in gastroduodenal ulceration, Palmer and Heinz,[1] in 1934, concluded that the usual stimulus is the free hydrochloric acid of the gastric content. Terauchi and Watanabe[2] in the same year reported a series of observations from which they concluded that the acidity of the gastric juice is greater in duodenal than in gastric ulcer. In 1935 Delfino[3] attempted to attribute diagnostic significance to the curves for acidity

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1. Palmer, W. L., and Heinz, T. E.: The Mechanism of Pain in Gastric and Duodenal Ulcers: VII. Further Observations, Arch. Int. Med. **53**:269 (Feb.) 1934.

2. Terauchi, Y., and Watanabe, K.: The Stomach Juice in Patients Suffering from Gastric and Duodenal Ulcers, Jap. J. Gastroenterol. **6**:46, 1934.

3. Delfino, V.: A Contribution to the Study of Gastric Acid Secretion by Means of Fractional Analyses in Cases of Gastric and Duodenal Ulcers, Pathologica **27**:261 (April 15) 1935.

of ulcer-bearing patients, as compared with those of normal persons as determined by fractional test meals.

Hurst's [4] observations were the first to indicate the importance of increased intragastric tension in the production of distress in patients with ulcer and definitely minimized the acid factor. Ivy,[5] Smith and Paul,[6] Carlson,[7] Hardt [8] and others have concurred in observations that altered motor function resulting from spasm, particularly of the pylorus or of sensitized areas in the region of the ulcer, hyperperistalsis or a combination of these factors are concerned in the production of pain. Palmer [9] reported that he was able to reproduce characteristic pain in patients with peptic ulcer under suitable conditions of susceptibility by the administration of 0.5 per cent solution of hydrochloric acid and in some cases with lower concentrations. In a further study he [10] suggested the use of this procedure as a diagnostic test. Hardy [11] was unable to confirm Palmer's observations in a large series of patients.

Passing rubber balloons into the pyloric region of the stomach, Smith and Paul [6] found that in each instance pain corresponded with the passage of a peristaltic wave, except in the instances of more severe pain, when there was apparent spasm of the pylorus. Such evidence is difficult to correlate with the theories of the school of Talma, Bönniger, Heusche, von Selms, Sippy, Jordan and Palmer, which emphasizes gastric acidity as the fundamental mechanism of pain in patients with ulcer.

In analyzing the abundant but controversial data in the literature on levels of gastric acidity in patients with peptic ulcer, we find that there have been no reports of repeated examinations of the gastric contents of individual patients over periods of from two to five years. The

4. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929, p. 26.

5. Ivy, A. C.: Physiology of the Stomach: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920.

6. Smith, F. M., and Paul, W. D.: Studies on the Mechanism of the Pain in Peptic Ulcer, Ann. Int. Med. **5**:14, 1931.

7. Carlson, A. J.: Origin of Epigastric Pains in Cases of Gastric and Duodenal Ulcer, Am. J. Physiol. **45**:81, 1917.

8. Hardt, L. L. J.: Studies of the Cause of Pain in Gastric and Duodenal Ulcers: II. Peristalsis as the Direct Cause of Pain in Gastric Ulcers with Achylia and in Duodenal Ulcers, Arch. Int. Med. **29**:684 (May) 1922.

9. Palmer, W. L.: The Mechanisms of Pain in Gastric and Duodenal Ulcers: II. The Production of Pain by Means of Chemical Irritants, Arch. Int. Med. **38**: 694 (Dec.) 1926.

10. Palmer, W. L.: The "Acid Test" in Gastric and Duodenal Ulcer: Clinical Value of Experimental Production of Typical Distress, J. A. M. A. **88**: 1778 (June 4) 1927.

11. Hardy, T. L.: The Rôle of Hydrochloric Acid in the Causation of Gastric Pain, Lancet **1**:711 (April 6) 1929.

Correlation of Individual Cases

Case No.	Symptoms First Appeared (Year)	Degree of Intractability	Weeks of Observation	Number of Gastric Analysis	Average Free Acid Level	Highest Free Acid Level	Lowest Free Acid Level	Recurrence During Study	Season of Recurrence: Winter	Spring	Summer	Fall	Acid Trend Just Prior to Recurrence: Higher	Lower	Not Significant	Acid Trend During Recurrence: Higher	Lower	Not Significant	Acid Trend During Distress: Higher	Lower	Not Significant
1	1928	++++	185	61	63.6	113	24	6	0	3	0	3	3	2	1	3	1	2	1	6	2
2	1921	++++	164	43	13.0	71	0	6	1	2	1	2	0	2	4	2	1	3	2	2	4
3	1926	++++	180	65	32.3	75	0	8	3	1	2	2	4	4	0	2	4	2	3	14	0
4	1930	+++	125	48	24.5	58	0	5	1	1	1	2	4	1	0	1	4	0	3	3	1
5	1924	++++	127	48	47.0	106	11	5	1	1	1	2	5	0	0	1	4	0	2	3	1
6	1915	++++	92	52	43.1	71	12	3	0	1	0	2	2	0	1	1	2	0	1	0	6
7	1931	++++	150	71	36.2	83	12	7	0	2	2	3	5	2	0	0	5	2	0	5	1
8	1923	++++	147	41	46.0	84	30	6	0	2	1	3	2	3	1	1	3	2	2	3	2
9	1923	++++	120	64	49.2	157	0	4	1	0	1	2	1	2	1	3	0	1	3	2	0
10	1930	+++	241	70	30.0	70	2	6	1	3	1	1	1	3	2	3	1	2	2	4	1
11	1917	++++	73	49	37.1	63	2	4	2	0	0	2	1	2	1	0	2	2	2	0	2
12	1923	+++	117	49	42.6	74	2	3	0	1	0	2	1	1	1	2	0	1	3	0	0
13	1928	+++	152	32	34.1	75	2	2	0	1	0	1	2	0	0	0	2	0	1	1	1
14	1927	++++	161	30	51.3	99	24	4	1	2	0	1	2	1	1	2	2	0	1	3	1
15	1925	++++	196	66	38.4	88	13	4	1	1	1	1	1	2	1	0	3	1	2	3	1
Average 11.3 yr.			148.6	53.2	39.2	85.8	8.9	4.8													
Totals									12	21	11	29	34	25	14	21	34	18	28	51	23
Control Series																					
16			152	37	29.7	59	4														
17			182	32	25.5	58	9														
18			180	56	27.7	51	0														
19			109	70	43.0	93	0														
20			142	52	32.5	55	7														
Average			153.0	49.4	31.0	63.2	4.0														

Total duration of observation, wk.	2,995.0
Average duration of observation, wk.	150.8
Total number of recurrences during study	73.0
Total number of gastric analyses	1,036.0
Average number of gastric analyses per patient	51.8

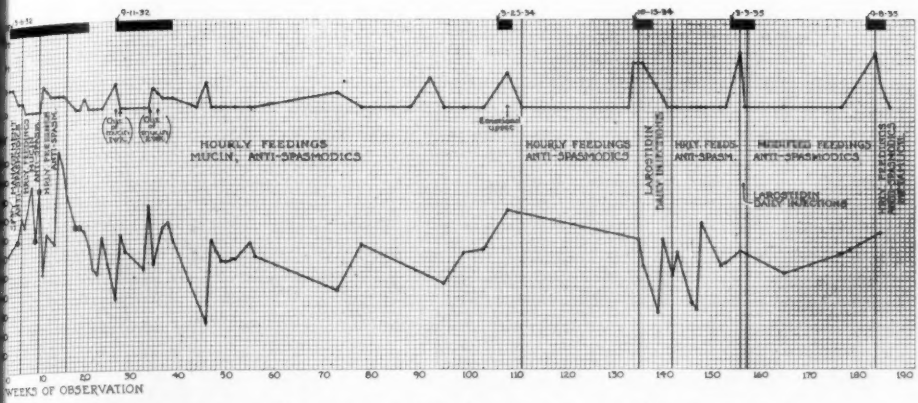

Chart 1.—S. S., a white man aged 40, had a typical history of ulcer. He had received alkaline powders for several months prior to admission to the hospital. He showed marked emotional instability. Each recurrence was preceded by infection of the upper respiratory tract, a boil (in one instance) or an emotional upset. This patient was studied for three years and seven months. In charts 1 to 10 the encircled dot indicates a positive reaction to the benzidine test. The blackened areas indicate activity of the ulcer. The term larostidin, used in several charts, is the trade name for a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. Mucilose is a proprietary hemicellulose preparation obtained from Plantago Loeflingi (related to psyllium). Metamucil is a similar preparation, obtained from Plantago ovata.

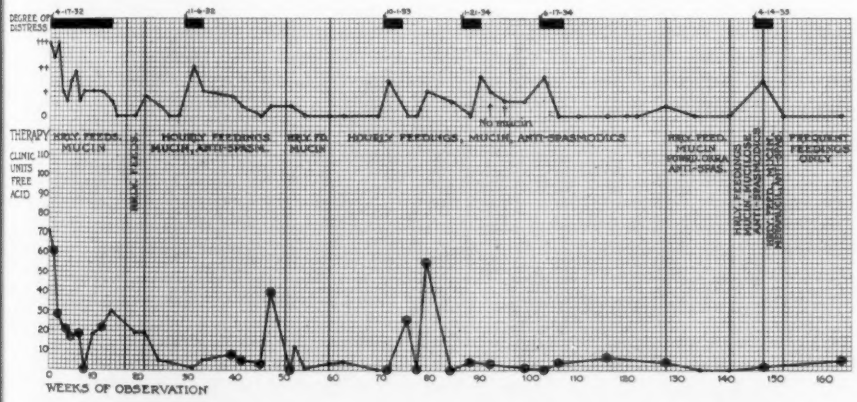

Chart 2.—A. E., a white man aged 32, had a perforated ulcer in 1928. He was on Sippy management for one year prior to admission to the hospital. Each recurrence, with one exception, followed an infection of the upper respiratory tract. This patient was studied for three years and two months.

patient is seldom observed until after the ulcer has arrived. The objective of our study was to determine the trend of free acid in patients with gastroduodenal ulcerative disease during periods of recurrence and remission, to investigate the relationship between the levels of acidity and the appearance of distress and to evaluate the response of gastric acidity to therapy over long intervals.

METHODS AND MATERIAL

The patients selected for this study were regularly seen in the clinic for patients with gastro-intestinal disorders in the outpatient department of St. Luke's Hospital. The criteria for selection were the duration of observation, the degree of intractability of the ulcer and the number of gastric analyses performed for each patient. All the patients were ambulatory during the study and were followed at regular

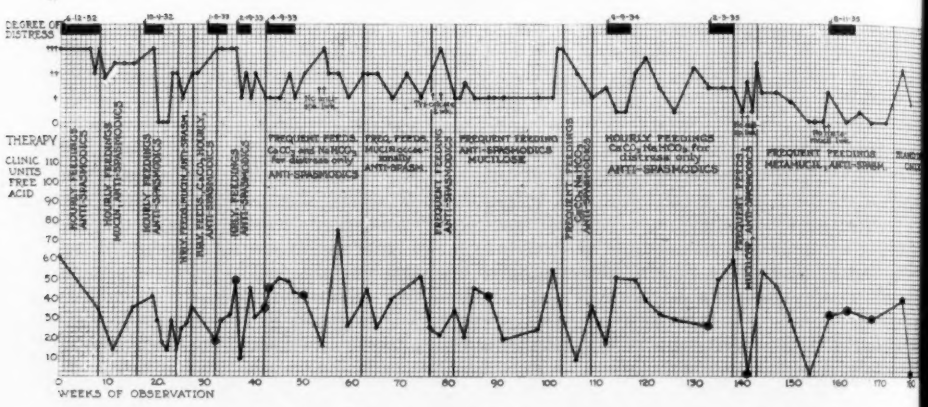

Chart 3.—E. B., a white man aged 26, had an appendectomy in 1926 for relief of ulcer-like distress, with no success. A diagnosis of duodenal ulcer was first made in 1927. Since then he had been attended by nine physicians, three of whom advised surgical intervention. This patient was studied for three years and eight months. Calcium carbonate and sodium bicarbonate were administered as indicated.

In the seventy-fifth week tri-calsate, a proprietary preparation containing tribasic calcium phosphate $Ca_3(PO_4)_2$ and sodium citrate, was administered.

intervals by means of gastric analyses, stool examinations and roentgenologic studies. A few patients were hospitalized for short periods. These intervals have been indicated in the individual graphic analyses.

Of the twenty patients reported on in this series, fifteen had duodenal ulcer and five were controls, in whom no ulcer could be demonstrated but who received ulcer therapy similar to that given the patients with duodenal ulcer. The average time of observation for each patient was one hundred and fifty and eight-tenths weeks. A total of one thousand and thirty-six gastric analyses were performed, with an average of fifty-one and eight-tenths Ewald test meals per patient. The average duration of symptoms in the patients with duodenal ulcer was eleven years.

A second group of patients were maintained on one form of therapy and studied at intervals by means of eight hour fractional gastric analyses. We wished to determine whether any sustained reduction in gastric acidity could be obtained by continued use of the Sippy or other forms of management.

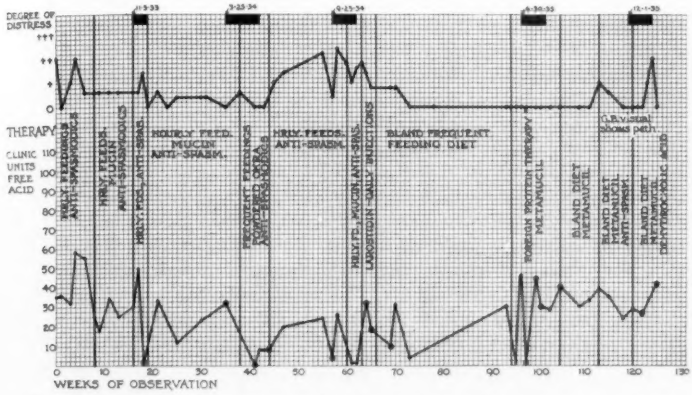

Chart 4.—J. S., a white man aged 43, had a typical history of ulcer. Chronic hypertrophic arthritis and chronic cholecystitis were complicating factors. This patient was studied for two years and five months. In November 1935 roentgenologic evidence of a pathologic condition of the gallbladder was obtained.

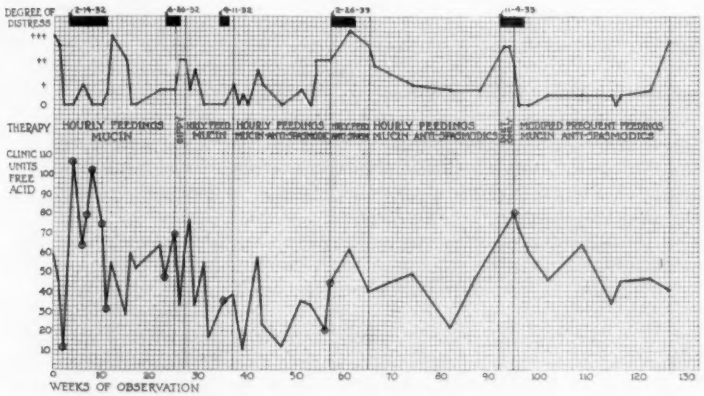

Chart 5.—H. C., a Negro aged 39, had a typical history of ulcer of seven years' duration. Previously he had been treated at several other clinics, with dietary management and alkaline powder. This patient was studied for two years and five months.

The routine Ewald test meal used in the analyses consisted of four crackers and two glasses of water. Aspiration of the stomach contents was performed after an interval of forty-five minutes. The stomach contents were analyzed for free, com-

bined and total acid and for blood by routine laboratory methods. Previous to each test meal the patient had abstained from food, alkaline powders, mucin or any other medication for at least twelve hours.

The criteria on which recurrences of the activity of the ulcer were based in his study were purely objective: (1) the presence of blood in the gastric contents, (2) the presence of blood in the stools, (3) a marked increase in tenderness on abdominal palpation, (4) an increase in deformity roentgenologically and (5) an increase in the gastric retention occurring with increased spasm in the area of the ulcer.

RESULTS

During the course of this study we were able to observe seventy-three recurrences of the activity of an ulcer. The duration of the recurrences varied among the patients, likewise the intervals of

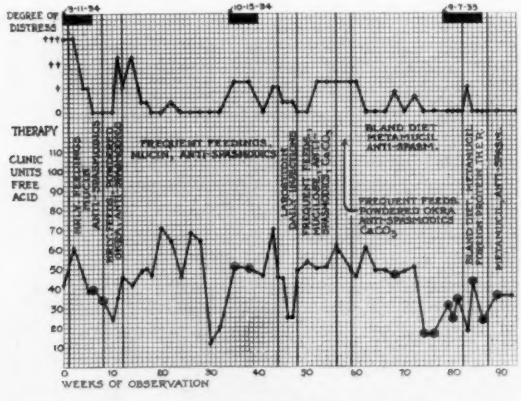

Chart 6.—T. C., a white man aged 47, had a typical history of ulcer. He was first seen during an attack of pyelitis. He was hospitalized during our observation for undulant fever, during which time he had a recurrence of ulcer. Recurrences seemed to be associated with infections of the upper respiratory tract. This patient was studied for one year and nine months. Calcium carbonate was administered during two periods of study.

quiescence between the flare-ups in activity. Certain general observations, however, seem of interest. Although some clinicians have previously commented on the apparent seasonal incidence of recurrences of ulcer, we have been unable to find figures on which the statements were based. In our series 68.5 per cent of the seventy-three recurrences took place during the spring and fall. The second general observation is the fact that in the majority of instances the recurrences followed the onset of an acute infection. For the most part these infections involved the upper respiratory tract, but recurrences were also noted after an acute abscess of a tooth, a carbuncle and in one instance infec-

tion of the hand. In other patients emotional stress and strain seemed to be of greater significance as the predominant factor in bringing on the recurrence.

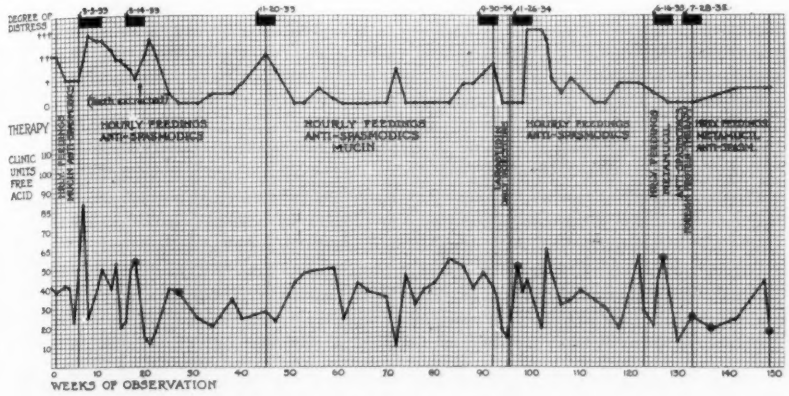

Chart 7.—F. L., a white man aged 46, had a typical history of ulcer, with prolonged use of alkaline powders prior to admission to the hospital. He showed marked emotional instability. This patient was studied for three years.

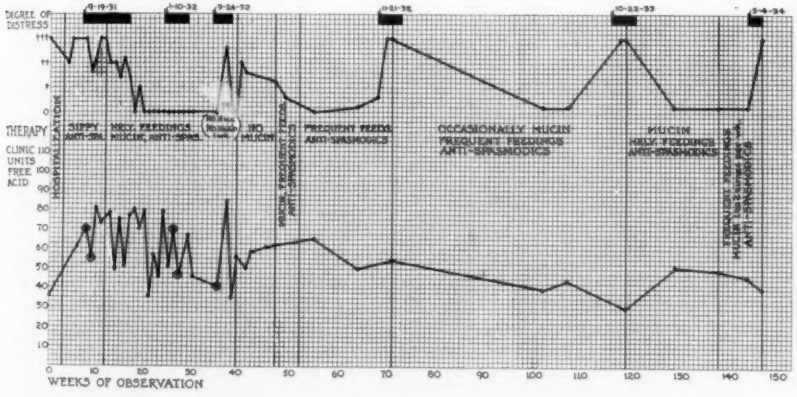

Chart 8.—N. H., a Negro aged 40, had a typical history of ulcer. Prior to admission to the hospital this patient had been hospitalized for management of ulcer for a total of one hundred and twelve days. He was studied for two years and eleven months.

The data demonstrate that the trend of gastric acidity bears no definite relationship to the onset of a recurrence. A rise in the level for free acid was observed prior to the recurrence of activity of the

ulcer in 46.5 per cent of the seventy-three recurrences. In 34.2 per cent, however, the values for acid were lower than the preceding levels, and in the remainder no significant change in acidity was observed. The chief point of interest is the fact that *in the same patient* the level of

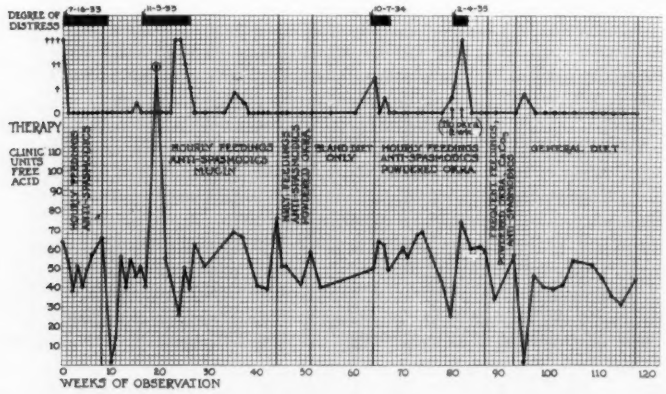

Chart 9.—D. H., a white man aged 47, had a typical history of ulcer. Two of the four recurrences were preceded by infection of the upper respiratory tract. Since January 1934 the patient had been working as a street laborer. He was studied for two years. In April and May 1935 calcium carbonate was administered.

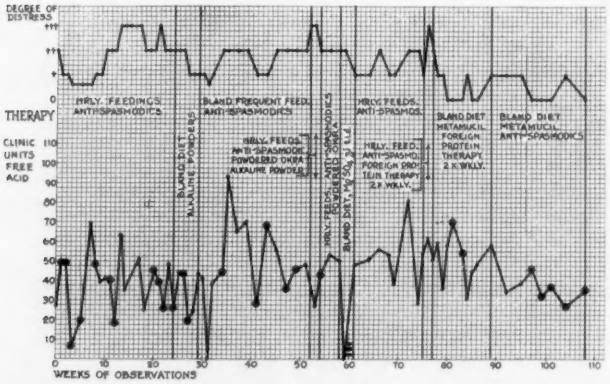

Chart 10.—L. A., a white man aged 48, was studied as a control. Thorough roentgenologic and laboratory studies revealed no basis for a diagnosis of duodenal ulcer. This patient had a so-called pseudo-ulcer syndrome. He was studied for two years and one month. From the fifty-ninth to the sixty-first week magnesium sulfate was administered, together with a bland diet.

free acid may rise, fall or undergo no alteration prior to a recurrence. Conversely, there were marked rises in the level of free acidity repeatedly without recurrence.

Similar fluctuations of the levels for gastric acid were observed during the periods of recurrence. The accompanying table shows the finding that in some patients the level for free acid falls during a recurrence. In other patients in a smaller number of instances there was a higher level for free acid during a recurrence than before it. In still others no significant change in free acidity was observed. Even for the same patient there was no constant behavior of the acid level during a recurrence. During one recurrence the acid level may be higher than its previous value, whereas in subsequent recurrences the

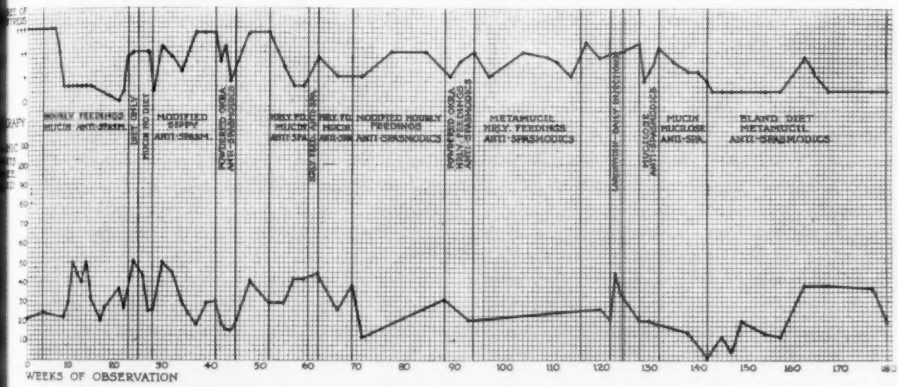

Chart 11.—S. B., a white man aged 32, was studied as a control. Thorough roentgenologic and laboratory studies revealed no basis for a diagnosis of duodenal ulcer. As with other patients in this group, this patient may be said to have shown a "pseudo-ulcer" syndrome. He was studied for three years and six months.

acid level may be lower or unchanged. The variations concerning each patient have been graphically arranged, examples being given in charts 1 to 9.

The level for free acid was found to bear no relation to the degree of distress manifested by the patients. In the intervals during which the patients experienced the greatest distress, 50 per cent of the acid levels were lower than during intervals when no distress was present. The occurrence of distress, as indicated by the individual charts, was furthermore shown to bear little or no relationship to the activity of the ulcer in most instances.

It will be observed that for two patients (cases 5 and 9) on several occasions high values for free acid were obtained, but at the same time the patients were totally free from distress. In these instances distress did not appear until the free acid had dropped to within normal limits. In one patient (case 2) it will be observed that distress was present at intervals despite the existence of almost complete achlorhydria.

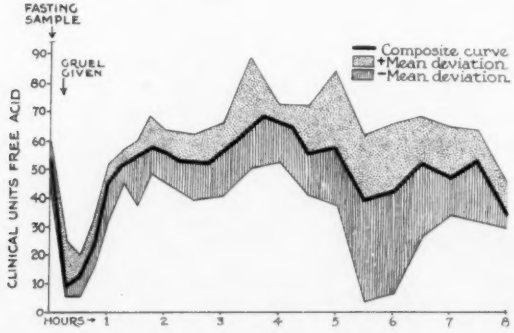

Chart 12.—A composite curve for the results of eight fractional gastric analyses made for control patient H. T. Nothing was administered during the test.

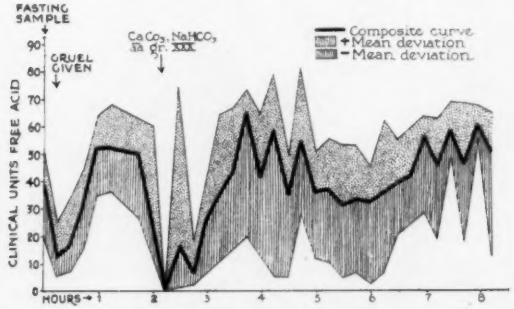

Chart 13.—A composite curve for the results of seventeen fractional gastric analyses made for control patient H. T. after administration of alkali (calcium carbonate and sodium bicarbonate).

Owing to the persistently low level for free acid and the continued presence of blood in the gastric contents, this patient was examined roentgenologically at frequent intervals for malignant growth. The present excellent health of this patient, together with normal laboratory findings, eliminates the diagnosis not only of a gastric malignant growth but of pernicious anemia and gastric syphilis.

The two individual charts (charts 10 and 11) for the control group of five persons demonstrate the wide variations of the acid level in normal persons. Antacid therapy did not noticeably change the gastric acidity of these normal controls. From the standpoint of therapy it will be seen that in both the group of ulcer-bearing patients and the control series all measures have little effect in bringing about a sustained reduction of the levels for free acid in the fasting state. Fewer recurrences and best subjective results were obtained with continued dietary management, with frequent feeding plus mucin therapy.

Charts 12 and 13 illustrate the typical findings for the group of patients studied by means of fractional gastric analyses. This particular patient was maintained on hourly feedings and hourly powders throughout the period of observation. No medication or feeding was administered for twelve hours preceding each test. It will be observed that there was no significant reduction in the fasting level of free acid, despite the fact that alkalis had been stopped only twelve hours previously. It will also be observed that no sustained fall in the level for free acid resulted from the use of alkali. In no instance were we able to demonstrate a sustained lowering effect on the acid level due to neutralization therapy. Similar tests were also made with histamine, and no significant alteration in gastric behavior could be observed.

COMMENT

We are well aware that the advent of some of the more recent studies of gastric secretion by means of fractional methods of analysis, especially those of Klumpp and Bowie,[12] Martini and Becker,[13] Fogelson [14] and others, places the status of the accuracy of the routine Ewald procedure in some doubt. Comfort and Osterberg [15] and Eusterman and Balfour [16] still favor the Ewald procedure as a routine method of investigation and further maintain that its relative accuracy is high. The more detailed technical methods were impracticable in the present study because of the number of patients in the series and the long periods of observation. While the values reported for acid therefore

12. Klumpp, T. G., and Bowie, M. A.: Studies on Gastric Secretion, J. Clin. Investigation **12**:1, 1933.

13. Martini, Paul, and Becker, K. P.: Absolute Tests of Gastric Function as Basis for Comparing Amount and Acidity of Gastric Secretion, Deutsches Arch. f. klin. Med. **175**:1, 1933.

14. Fogelson, S. J.: Personal communication to the authors, March 1936.

15. Comfort, M. W., and Osterberg, A. E.: Gastric Secretion After Stimulation with Histamine in Presence of Various Types of Gastric and Duodenal Lesions, J. A. M. A. **97**:1141 (Oct. 17) 1931.

16. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 158.

may be subject to moderate error, according to some workers, the extended observation and the large number of analyses for each patient compensate for the variations of the single test meal.

Indicating the degree of distress as well as the exact time and duration of the recurrences involved some difficulty. It is impossible to prove definitely whether or not a patient has an active ulcer, in spite of the conscientious use of the five criteria of diagnosis enumerated in a previous article.[17] Blood in the gastric contents, blood in the stools and frequent roentgenologic studies proved to be the best evidence of recurrence. No reliance could be placed on the presence of hyperacidity. We believe that gross aid is obtained from roentgen studies, despite the fact that roentgenologists have become more cautious in their estimation of the activity of an ulcer. The history of the ulcer and the response to therapy were considered but have less than their usual value for patients with intractable ulcers.

Fowler, Spencer, Rehfuss and Hawk [18] have shown that the stomach tends to bring its contents to a normal acid level regardless of the reaction of the ingested substance. Lockwood and Chamberlain,[19] Crohn [20] and others have reported similar observations. Rehfuss and Hawk [21] have reported that by means of fractional test methods they found evidence of the secretion of gastric juice of constant acidity in both normal and pathologic human subjects. While these investigations were carried on for brief intervals only, our data demonstrate that gastric acidity fluctuates from month to month and year to year without regard to therapy. Apparently the one constant feature is the fact that gastric acidity tends to moderate as the entire gastro-intestinal tract returns to normal.

Alvarez and Vanzant [22] have previously indicated that in some persons the variations in gastric secretion are so wide that little value can

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17. Brown, Clarence F. G.; Cromer, S. P.; Jenkinson, E. L., and Gilbert, N. C.: Mucin Therapy for Peptic Ulcer, J. A. M. A. **99**:98 (July 9) 1932.

18. Fowler, C. C.; Spencer, W. H.; Rehfuss, M. E., and Hawk, P. B.: Gastric Analysis: IV. The Gastric Equilibrium Zone, J. A. M. A. **77**:2118 (Dec. 31) 1921.

19. Lockwood, B. C., and Chamberlain, H. G.: The Effect of Alkalis on Gastric Secretion and Motility as Measured by Fractional Gastric Analysis, Arch. Int. Med. **32**:74 (July) 1923.

20. Crohn, B. B.: Effect of Antacid Medication on Gastric Secretion and Acidity, Am. J. M. Sc. **155**:801, 1918.

21. Rehfuss, M. E., and Hawk, P. B.: Direct Evidence of the Secretion of Gastric Juice of Constant Acid Concentration by the Human Subject, J. A. M. A. **63**:2088 (Dec. 12) 1914.

22. Vanzant, F., and Alvarez, W. C.: What Is the Value of Our Gastric Analysis? A Study of the Daily Variations in the Gastric Acidity of Two Normal Persons, Proc. Staff Meet., Mayo Clin. **6**:419 (July 15) 1931.

be attached to one test meal. The futility of a single test meal for diagnostic purposes is clearly demonstrated in our series of normal and ulcer-bearing persons.

The height of the acid level bears no relation to the degree of distress manifested by the patient on the basis of our findings. Any therapeutic procedure seems to produce temporary relief in some cases. We were unable to concur with Palmer's correlation between acid levels and the onset of distress. It appears therefore that the individual's inherent mechanisms of gastric defense control the levels of gastric acidity, and little can be done fundamentally by means of neutralization therapy.

We are now putting into practical use the concrete evidence of the frequency of recurrence during the spring and fall months. During these months patients with intractable ulcer under our observation are placed on careful dietary management, and gastric mucin is included as a prophylactic measure. In many instances this procedure seems effective. Thus far, however, the available data indicate that the seasonal frequency of recurrences of ulcer in patients with intractable ulcer has been definitely reduced.

CONCLUSIONS

There is no significant trend in the gastric acidity prior to a recurrence of activity of an ulcer. In the same patient the level for free acid may rise, fall or undergo no significant change before recurrence.

During a recurrence of activity, gastric acidity undergoes no constant variation. Upward or downward fluctuations occur in the same patient.

Definite evidence was obtained indicating a seasonal occurrence of activity of ulcers. Of seventy-three recurrences observed in this study, 68.5 per cent occurred during the spring and fall months.

The height of the level for free acid bears absolutely no relationship to the degree of distress manifested by the patient. Conversely, the acid levels were lower than the preceding levels 50 per cent of the time during occurrence of the greatest distress.

The degree of distress may in no way be a criterion of the activity of an ulcer. The patient may have every symptom of recurrence but have no ulcer. He may have no subjective symptoms and yet may have a highly active ulcer. Criteria of recurrence, therefore, must be objective, not subjective.

CENTRAL NERVOUS SYSTEM AND SUGAR METABOLISM

CLINICAL, PATHOLOGIC AND THEORETICAL CONSIDERATIONS, WITH SPECIAL REFERENCE TO DIABETES MELLITUS

A. R. VONDERAHE, M.D.
CINCINNATI

Since the discovery of insulin the treatment of diabetes mellitus has made remarkable strides. Many factors underlying the causation of the disease, however, remain obscure. The associated anatomic changes are for the most part the result of an excess amount of sugar in the blood and are thus the effects rather than the causes of the disease. It is true that changes in the pancreas occur with great frequency, but these are not constant. In a study of 229 diabetic patients Warren [1a] noted that the pancreas showed fibrosis, hyaline degeneration, hypertrophy, hydropic degeneration, pyknotic nuclei, hemorrhage or adenoma in the islands of Langerhans in 190 patients while in 69 patients it was normal. The author [1b] stated:

> These cases in which changes in the pancreas are absent or too trifling to merit consideration have always puzzled and irritated the pathologist. It is difficult to conceive of long-continued and profound functional pathology without organic change, the field of mental disease excepted.

In explanation of these observations Warren [1c] suggested three hypotheses:

> (1) The islands may be normal and insulin may be produced, but is either defective in quality or is neutralized by some substance in the body; (2) the diabetes may be of other than insular origin, and (3) the insulin may be formed normally by normal islands, but through failure in transport the insulin is not brought into the blood stream and so not distributed where its effects are needed. . . . Whichever (if any) one of these hypotheses is true, we must face the fact that cases of diabetes absolutely identical with one another from the clinical standpoint show no evidence of structural disease in the islands of Langerhans in one instance, and show marked injury of various types in still another.

Still more disturbing are this author's [1d] observations on the pancreas of 200 nondiabetic persons. One or more of the changes previously noted for diabetes were observed in 67 (or 16.5 per cent) of this series of nondiabetic persons.

From the Department of Anatomy (Neurology), the University of Cincinnati Medical School.

1. Warren, Shields: (*a*) The Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930, p. 42; (*b*) p. 198; (*c*) p. 53; (*d*) p. 72; (*e*) p. 194; (*f*) p. 196.

The absence of pathologic changes in the pancreas has led to the suggestion that pituitary disease may be responsible for a certain number of cases. Marie,[2] in 1889, noted diabetes in 2 of 4 patients with acromegaly, while the association of glycosuria with tumor of the hypophysis was described by Loeb[3] in 1898. Naunyn,[4] in 1906, suggested that these tumors effected their results by pressure on a hypothetic "sugar center." Cushing[5] reported a series of clinical observations and experiments pointing to the association of glycosuria with lesions of the pituitary body. Bailey and Bremer[6] and others showed that these findings could be produced experimentally by means of lesions of the hypothalamus, the pituitary body, its nerve connections and the blood supply remaining intact. White[7] and Joslin[8] presented some evidence of relationship of diabetes and changes in the pituitary body by calling attention to the occurrence of diabetes among children who were taller than ordinary.

Warren[10] studied the hypophyses of 27 diabetic patients who were free from stigmas of pituitary disease, and in none did he find significant variation from the normal. This observation tends to confirm the finding of Bailey and Bremer and others that the relationship of the pituitary body to diabetes is indirect, the primary metabolic center being in the hypothalamic area in close relation to the gland.

Observations by Cannon[9] indicated that the emotions of rage and terror are productive of glycosuria. Clinical observations in the course of diabetes indicate a loss of sugar tolerance due to mental strain. The "sugar puncture" of Claude Bernard, again, points to a close relationship between the central nervous system and the pancreas. The intermittent action of the adrenal gland in these cases must be borne in mind. Beattie and his collaborators[10] stated as their conclusion that the pos-

2. Marie, P.: Acromegaly: A Clinical Study, Progrès méd. **9**:189, 1889.

3. Loeb, M.: The Pituitary Body in Diabetes Mellitus, Zentralbl. f. inn. Med. **19**:893, 1898.

4. Naunyn, B.: Diabetes Mellitus, Vienna, A. Hölder, 1906.

5. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

6. Bailey, Percival, and Bremer, Frederick: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.

7. White, P.: Potential Diabetic Child, J. A. M. A. **88**:170 (Jan. 15) 1927.

8. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928.

9. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, ed. 2, New York, D. Appleton & Company, 1929.

10. Beattie, J.; Brown, G. R., and Long, C. N. H.: Physiological and Anatomical Evidence for Existence of Nerve Tracts Connecting Hypothalamus with Spinal Sympathetic Centers, Proc. Roy. Soc., London, s.B **106**:253 (May 3) 1930.

terior hypothalamic nuclei influence sugar metabolism through their influence on the secretion of epinephrine. As far as the adrenal bodies are concerned in the production of diabetes, Warren [1f] in a series of 300 autopsies observed no significant lesions in these glands.

That the nervous system plays a rôle in the alteration of sugar metabolism has been known for many years, particularly since Claude Bernard punctured the floor of the fourth ventricle and produced glycosuria. In the following case reports this effect is illustrated:

REPORT OF CASES

CASE 1.—*Traumatic subarachnoid hemorrhage at base of brain; glycosuria.*

A Negress aged 39 was admitted to the Cincinnati General Hospital in a state of unconsciousness after injury to the head. There was general muscular twitching. The deep reflexes were exaggerated. Urinary examination revealed an excessive amount of sugar. The patient died ten minutes after admission to

Fig. 1 (case 1).—Extensive subarachnoid hemorrhage, with especially severe involvement of the tuber cinereum.

the hospital. The history indicated that she had been in excellent health prior to the injury. A diagnosis of cerebral hemorrhage, probably traumatic, was made.

At autopsy an extensive subarachnoid hemorrhage was observed implicating all the structures at the base of the brain, including the tuber cinereum (fig. 1). Gross and histologic examination of the pituitary gland showed no abnormality.

Comment.—In this case there was evidence of the occurrence of a disturbance in sugar metabolism (glycosuria) in association with probable traumatic hemorrhage, implicating the tuber cinereum.

CASE 2.—*Essential hypertension; hemorrhage into pons, with pressure effects on third ventricle; glycosuria.*

A white woman aged 37 was examined in the outpatient dispensary of the Cincinnati General Hospital, and a diagnosis of essential hypertension was made. Several urinalyses made at various times showed no evidence of glycosuria. Subsequently the patient entered the hospital in a state of coma. The spinal fluid at the time was bloody. The urine showed an excessive amount of sugar.

At autopsy extensive hemorrhage was noted involving practically the whole substance of the pons, extending upward into the interpeduncular space and compressing the third ventricle (fig. 2).

Comment.—In this case there was evidence of a disturbance of the sugar-regulating mechanism from pressure effects on the hypothalamus or, more probably, from an interruption of the descending pathways from this area in the tegmentum of the pons.

Fig. 2 (case 2).—Hemorrhage involving the basal and tegmental portions of the pons, with rupture into the fourth ventricle.

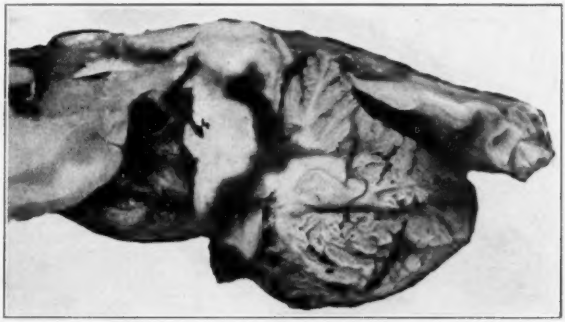

Fig. 3 (case 3).—Hemorrhage into the midbrain, with extension into the pons.

CASE 3.—*Cardiovascular renal disease; hemorrhage of midbrain; glycosuria.*

A 67 year old patient for several years attended the outpatient dispensary of the Cincinnati General Hospital because of hypertension. Repeated examinations of the urine showed no evidence of sugar at any time. After a "stroke of paralysis" the patient was brought to the hospital in a comatose state, presenting right hemiplegia. Urinalysis showed 4 + sugar. The patient died four days later.

At autopsy a hemorrhage was noted, having its origin in the left half of the midbrain and thrusting portions of the midbrain upward so as to compress the cavity of the third ventricle. Portions of the tegmentum of the midbrain and pons had been destroyed by the hemorrhage (fig. 3).

Comment.—The glycosuria in this case is regarded as due to compression of centers of carbohydrate metabolism in the hypothalamus or to destruction of the pathways from this area in the tegmentum of the midbrain.

CASE 4.—*Diabetes mellitus of increasing intensity; aphasia; psychosis; cyst of pulvinar of thalamus; obstructive internal hydrocephalus.*

A white woman aged 63 at the time of entrance into the Hamilton County Chronic Disease Hospital presented slight mental confusion, aphasia, speech

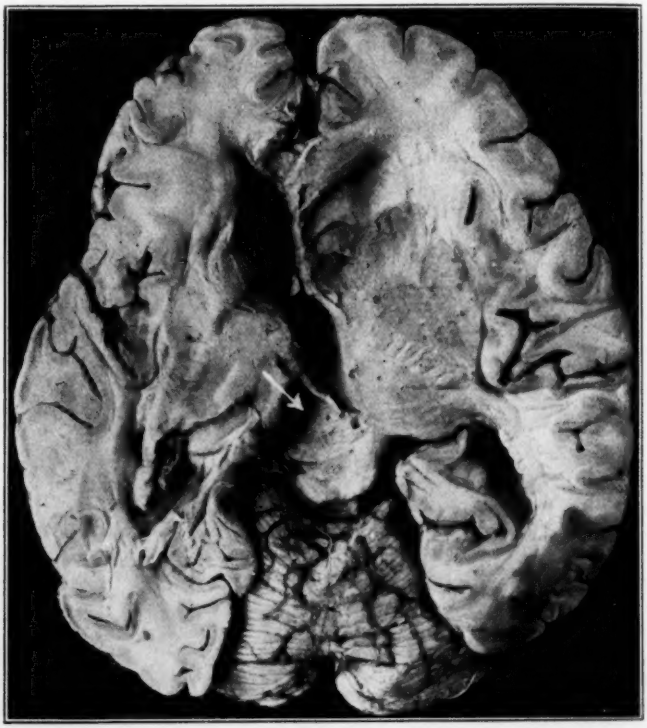

Fig. 4 (case 4).—The arrow indicates a cyst of the pulvinar of the thalamus which has grown mesially and caudally to erode the superior quadrigeminal body and to occlude the orifice of the aqueduct of Sylvius, producing internal hydrocephalus, which is especially marked in the third ventricle.

defect, incontinence of urine, weakness of the legs and diabetes mellitus. In the course of two months the glycosuria increased in intensity in spite of the administration of insulin. The psychotic manifestations increased in severity. Several days before death occurred the pupils became like pinpoints and fixed, and other neurologic signs developed. Four months prior to the patient's death a diagnosis of mild diabetes mellitus was made by Dr. Cecil Striker.

At autopsy a cyst of the pulvinar of the left thalamus was noted which had extended mesially and posteriorly to overlap and occlude the aqueduct of Sylvius, causing internal hydrocephalus, with marked dilatation of the third ventricle. On microscopic examination, in addition to other alterations, cell loss and retrograde changes were noted in the nucleus paraventricularis and in the substantia grisea of the hypothalamus (fig. 4).

Comment.—The origin of the diabetic state in this case may have been due to involvement of centers in the hypothalamus regulating sugar metabolism, or, if the cause existed elsewhere, the disease appeared to have been aggravated by pressure effects on this area.

CASE 5.—*Chronic duodenal ulcer; excessive alcoholism; psychosis; bleeding into intestine; hyperglycemia.*

A Negress aged 40 was admitted to the Cincinnati General Hospital complaining of extreme pain and soreness in the abdomen. Two months prior to her admission to the hospital a diagnosis of duodenal ulcer had been made at the outpatient dispensary, at which time a specimen of urine had shown no sugar. There had been excessive alcoholism for three months and rather constant alcoholic indulgence for many years. During the last three weeks the patient's mental state had been regarded as disturbed. There was a general downward course, with increasing weakness as bleeding from the bowels continued. A specimen of blood taken on the day of the patient's death for chemical study contained 299 mg. of sugar per hundred cubic centimeters.

At autopsy the diagnosis of a large duodenal ulcer was confirmed. Microscopic examination of the diencephalon revealed multiple hemorrhages in the anterior and superior aspects of the hypothalamus, implicating the superior portion of the nucleus paraventricularis. Multiple capillary hemorrhages were also present in the nucleus supra-opticus on both sides. There was marked destruction of many cells in the nucleus paraventricularis, and the remaining cells for the most part presented evidence of acute chromatolysis and other retrograde changes. There was appreciable cell loss in the substantia grisea of the third ventricle and in the nucleus tuberis lateralis, and throughout the entire gray matter of this area there was increased glial proliferation (fig. 5).

Comment.—This patient presented terminal hyperglycemia associated with recent capillary hemorrhages in the anterior portion of the hypothalamus implicating most prominently the nucleus paraventricularis.

RÔLE OF THE CENTRAL NERVOUS SYSTEM IN THE REGULATION OF SUGAR METABOLISM—A HYPOTHESIS

Recently Morgan, Malone and I[11] studied cellular changes in the hypothalami of 15 patients with diabetes mellitus, using as controls the

11. Morgan, L. O.; Vonderahe, A. R., and Malone, E. F.: Pathological Changes in the Hypothalamus in Diabetes Mellitus, J. Nerv. & Ment. Dis. **85**:125, 1937.

brains of 5 nondiabetic patients for whom the causes of death were as follows: (1) malignant hypertension, (2) septicemia, (3) gunshot wound in the back, (4) pulmonary tuberculosis and (5) mercury bichloride poisoning. The results of this study indicated a constant loss of cells, ranging from 30 to 65 per cent, in the nucleus paraventricularis in all the patients with diabetes. In the remaining cells of this

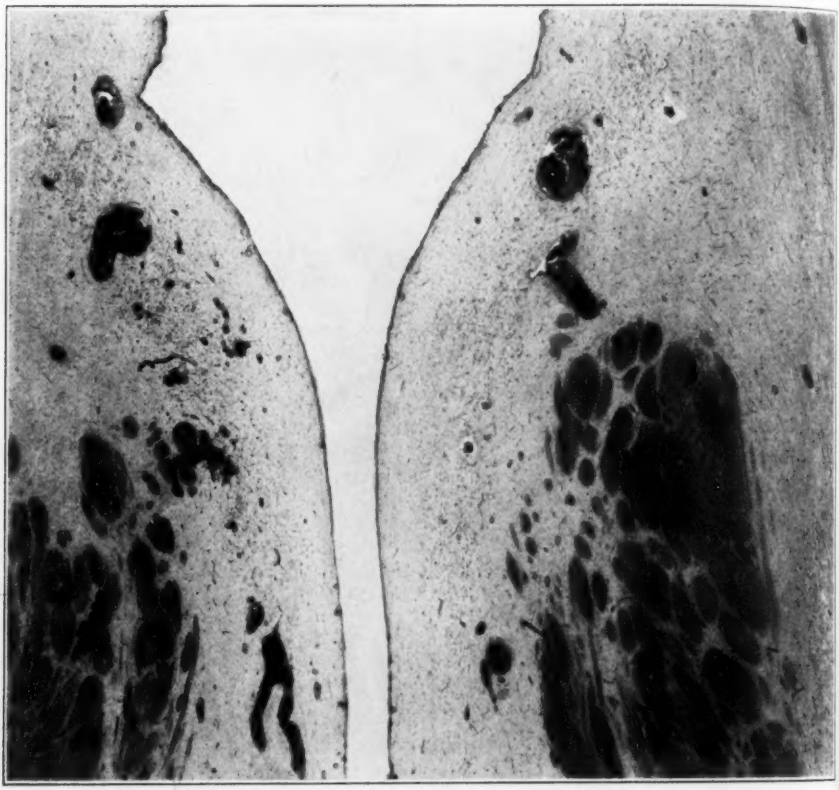

Fig. 5 (case 5).—Multiple venous hemorrhages with smaller capillary and arteriolar hemorrhages may be noted in the superior anterior portion of the hypothalamus between the ependyma and the fornix and implicating the nucleus paraventricularis. Morgan's stain; × 25.

nucleus marked retrograde changes tended to occur. In 6 of the 15 patients there was, in addition to the aforementioned changes, severe cell loss in the substantia grisea of the third ventricle and in the nucleus tuberis lateralis, associated with a considerable amount of retrograde

change in the remaining cells of these nuclei. In the latter group of patients a psychosis was associated with the diabetes mellitus; this finding corresponds to that noted in the previous work of Morgan and Gregory,[12] in which cell loss in the nucleus tuberis lateralis and in the substantia grisea of the third ventricle was observed in a group of 32 psychotic patients presenting in common the presence of mental deterioration. With a single exception, the changes in the diabetic patients were much milder than those in the deteriorated psychotic patients.

Utilizing these data and those obtained from the patients in the present series it is possible to construct a working hypothesis for a phase of the regulation of sugar metabolism by the central nervous

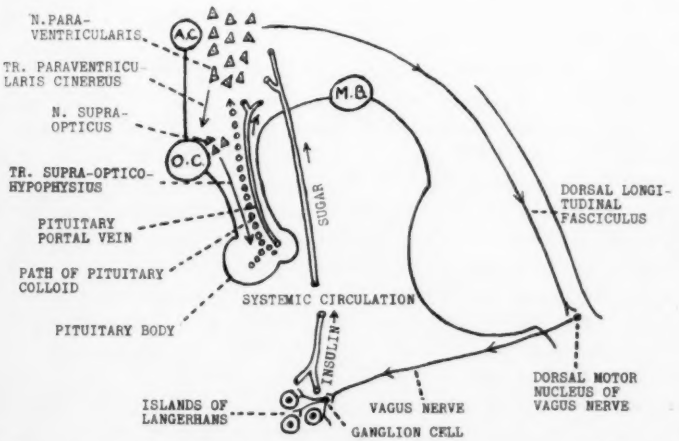

Fig. 6.—Diagram explaining the rôle of the nucleus paraventricularis of the hypothalamus in the regulation of sugar metabolism. *A.C.* indicates the anterior commissure; *O.C.*, the optic chiasm, and *M.B.*, the mammillary body. The pathways for the stimulation of insulin by way of the thoracolumbar sympathetic system, with the probable superior center in the posterior portion of the hypothalamus, are not indicated in the diagram. Further explanation is given in the text.

system (fig. 6). One may recall that the nucleus paraventricularis is connected by fiber paths to the nucleus supra-opticus, which in turn is connected by fiber paths to the posterior lobe of the pituitary body. Again, the pituitary body sends some of its secretion directly into the hypothalamus (Collin[13]), and some of the secretion may be carried

12. Morgan, L. O., and Gregory, H. S.: Pathological Changes in the Tuber Cinereum in a Group of Psychoses, J. Nerv. & Ment. Dis. **82**:286, 1935.

13. Collin, Rémy: The Functional Relationship Between the Pituitary Body and the Tuber Centers, Ann. de méd. **18**:428, 1925.

to the hypothalamic nuclei through a system of portal veins (Popa and Fielding [14] and Basir [15]). Also, there is the possibility that nerve fibers run from the pituitary body to the hypothalamic nuclei. There is an intimate connection, accordingly, between the nucleus paraventricularis and the pituitary body. Fibers leaving the nucleus paraventricularis pass downward close to the wall of the ventricles in the dorsal longitudinal fasciculus, or bundle of Schütz, to terminate about cells in the dorsal motor nucleus of the vagus nerve. Preganglionic fibers stream from this nucleus to ganglion cells in the pancreas. From here short postganglionic fibers form networks around the islands of Langerhans (peri-insular network of Gentes) and terminate in a wealth of minute fibrils on the island cells.[16] Gentes [17] emphasized the richness of these plexuses on island cells and stated that it distinguishes them from the cells of the pancreatic gland proper. Pensa [18] confirmed these observations.

The hypothesis proposed here regards the nucleus paraventricularis as a central stimulator of the production of insulin. The preceding work suggests that in addition to being stimulated by neural impulses, the cells of this nucleus are stimulated also by the presence of sugar, just as the neurons constituting the respiratory center are stimulated by the presence of carbon dioxide. It is assumed that an excess of sugar in the blood activates these cells, resulting in the sending of impulses to the islands of Langerhans over the pathways described, thereby causing an increased production of insulin. The insulin causes a lowering in the sugar content of the blood, and the paraventricular nucleus comes to rest. If an excess of blood sugar from any cause continues, the syndrome of diabetes mellitus is produced; the paraventricular nucleus then is overworked, its cell bodies show evidence of fatigue and they finally die, so that cell counts indicate a significant loss in number.

From an anatomic standpoint the pituitary body appears to be capable of influencing carbohydrate metabolism not only by the effect of its internal secretion in the blood but by the direct effects of its secretion on the cell groups in the hypothalamus. It is likely that the

14. Popa, G., and Fielding, U.: The Vascular Link Between the Pituitary and the Hypothalamus, Lancet **2**:238 (Aug. 2) 1930; The Portal Circulation from the Pituitary to the Hypothalamic Region, J. Anat. **65**:88, 1930.

15. Basir, M. A.: The Vascular Supply of the Pituitary Body in the Dog, J. Anat. **66**:387, 1932.

16. Greving, R., in Müller, L. R.: Lebensnerven und Lebenstriebe, Berlin, Julius Springer, 1931, p. 112.

17. Gentes, B.: Note on the Nerve Terminations in the Islands of Langerhans, Compt. rend. Soc. de biol. **54**:202, 1902.

18. Pensa, A.: Observation on the Description of Blood Vessels and Nerves to the Pancreas, Internat. Monatschr. f. Anat. u. Physiol. **22**:90, 1905.

effect of the pituitary body on the nucleus paraventricularis is inhibitory, with the result that excessive pituitary secretions may repress the production of insulin and cause a rise in the sugar content of the blood. Conversely, interference with the influence of the pituitary body may activate the production of insulin. Thus, Davis, Cleveland and Ingram [19] found that lesions properly placed in the hypothalamus would ameliorate the symptoms of pancreatic diabetes and prevent the glycosuria and hyperglycemia produced by stimulation of the superior cervical ganglion.

As noted previously, the islands of Langerhans receive, in addition to the fibers from the vagus nerve, postganglionic fibers from the thoracolumbar sympathetic system. Beattie and others have shown that the posterior hypothalamic cell groups are concerned with sympathetic effects. The conversion of glycogen into sugar and the increased production of insulin with the sympathetic emotions anger and rage have been demonstrated by Cannon.[9] This function, associated as it is with strenuous emotion or with severe exertion, is by nature of short duration or even of infrequent occurrence; while the effect of the parasympathetic (vagal) system is by nature anabolic and relatively constant in action.

The hypothesis proposed here recognizes that alterations of sugar metabolism may be caused in various ways, one of which is a disturbance in the central nervous system; by regarding the physiology of carbohydrate metabolism as a cycle in which the nervous system is one factor it provides for *effects* in the nervous system of continued hyperglycemia and so affords an explanation of numerous clinical phenomena of diabetes mellitus. It is not inconsistent with any rôle that the pituitary body, adrenal gland or any other internal secreting gland may play in the disorder.

In conclusion, it is important to point out that the effect of the nervous system is one of *modifying* certain intrinsic physiologic and chemical reactions which constitute essential sugar metabolism. That the internal glands, too, act merely in modifying this intrinsic mechanism is strikingly illustrated by the Houssay dogs, in which sugar metabolism proceeds more normally again when, after the removal of the pancreas, the pituitary body also is removed.

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19. Davis, L.; Cleveland, D., and Ingram, W. R.: Carbohydrate Metabolism: The Effect of Hypothalamic Lesions and Stimulation of the Autonomic Nervous System, Arch. Neurol. & Psychiat. **33**:592 (March) 1935. Cleveland, D., and Davis, L.: Further Studies on the Effect of Hypothalamic Lesions upon Carbohydrate Metabolism, Brain **59**:459, 1936.

SUMMARY

The proper understanding of diabetes mellitus as a clinical entity requires the inclusion of the central nervous system. Available evidence does not justify a view that diabetes mellitus is invariably caused by a lesion of the central nervous system. But clinical and pathologic data indicate that the nervous system becomes an integral factor in the cycle of events which constitute the phenomena of this disease. A hypothesis is proposed which assumes that the nucleus paraventricularis in the hypothalamus is stimulated by the presence of sugar to activate the cells of the islands of Langerhans to the production of insulin, and an analogy is suggested between this mechanism and the stimulation of the cells of the respiratory center by carbon dioxide. This hypothesis has been applied to patients with diabetes mellitus without gross cerebral lesions and to patients with various lesions of the brain, confirmed at autopsy, and presenting in common hyperglycemia or glycosuria.

Progress in Internal Medicine

GASTRO-ENTEROLOGY IN 1936

SELECTED TOPICS

GARNETT CHENEY, M.D.
SAN FRANCISCO

Instead of attempting to cover the whole field of gastro-enterology for 1936, I have selected four topics of major importance for review for this year. All deal with the stomach. The first is gastroscopy. It demands attention not only as a diagnostic procedure but because it is making possible a better understanding of many conditions affecting the gastric mucosa which have not been fully appreciated previously. The second is gastritis. The renewed interest in this disease has come about largely through the facility with which the gastric mucous membrane may now be directly observed through the flexible gastroscope. The third is the histidine treatment of peptic ulcer. This new therapeutic procedure for a long-recognized clinical condition was reviewed two years ago, while in its infancy. The large number of articles on this subject which have appeared in all parts of the world since then make possible now a more mature judgment of the efficacy of a form of treatment which sprang from an extremely flimsy experimental basis. The fourth concerns the experimental production of gastric erosions (ulcers) by means of a deficient diet and the prevention of the occurrence of the lesions by the supplying of certain dietary substances. This subject has as yet received no attention in medical research but in my opinion offers a fertile new line of investigation of certain gastric disorders.

GASTROSCOPY

The rigid gastroscope has been in use since the last century. Many drawbacks have prevented its general application to the study of gastric disease. Within the last few years a flexible gastroscope has been developed, which may be readily passed and which gives a really excellent view of the interior of the stomach. For the detailed technic of gastroscopic examination the original articles should be consulted. The method and the advantages to be derived therefrom have occupied the attention of a number of observers during the past year.

In a rather long but interesting discussion of gastroscopy Kalpen [1] traces the history of its development from "the wish" of Hippocrates to its fulfilment in the perfection of a flexible gastroscope in 1932 by

1. Kalpen, E.: Zur Licht und Instrumententechnik in der Gastroskopie, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **44**:157, 1936.

Wolf and Schindler. A fundamental problem in gastroscopy as well as in all forms of endoscopy has been the development of proper illumination. The solution of this problem, along with many other technical difficulties, is given in some detail, together with a number of illustrative figures.

Kerkhof [2] describes gastroscopy as another method of examining the stomach. He states that it is not a distressing examination for the patient, and as far as the gastroscopist is concerned it is not a difficult procedure. He would "much rather pass a gastroscope than a stomach tube." For all practical purposes gastroscopy is without danger. One patient with an early cancer on the posterior wall of the stomach near the greater curvature was successfully operated on when roentgen examination twice gave negative results although a lesion was definitely recognized through the gastroscope. Grossly the lesion appeared benign, but the microscopic examination proved it to be malignant.

The indications and contraindications for gastroscopy and the technic of the procedure are described by Symonds.[3] Contraindications are either extrinsic, such as aortic aneurysm, enlargement of the thymus or some other mediastinal tumor and disease of the spine interfering with its mobility, or intrinsic, such as advanced organic disease, extensive varicosities of the esophagus and acute esophagitis. The indication for gastroscopy is any persistent or unexplained symptom referable to the stomach. Of special interest are all forms of gastritis, gastric symptoms with negative roentgen findings, gastric neurosis, unexplained gastrointestinal hemorrhage, peptic ulcer and gastric cancer, particularly when the differential diagnosis between the last two is involved. The technic is outlined in detail.

Chevalier L. Jackson [4] describes the procedure of gastroscopy with the flexible gastroscope. He concludes that this instrument marks a new era in the endoscopic study of the stomach and that every "good gastroenterologist" will make gastroscopy a part of the routine study of his patients. However, he considers the use of the flexible instrument only an addition to the use of the rigid instrument when in the hands of the peroral endoscopic specialist.

Schindler [5] also describes the examination of the stomach with a flexible gastroscope and presents its advantages. This report is of particular interest because of the author's ingenuity in developing this instrument. The discussion is well worth reading.

2. Kerkhof, A.: Gastroscopy, Another Way of Examining the Stomach, Minnesota Med. **19**:647, 1936.

3. Symonds, C. W.: Gastroscopy: Indications, Contraindications, Technic, Arch. Phys. Therapy **17**:574, 1936.

4. Jackson, C. L.: Gastroscopy with the Flexible Gastroscope, Ann. Otol. Rhin. & Laryng. **44**:1150, 1935.

5. Schindler, R.: Gastroscopy with a Flexible Gastroscope, Am. J. Digest. Dis. & Nutrition **2**:656, 1936.

A consideration of the present status of gastroscopy from many points of view is presented by Schloss.[6] He describes the procedure as the intravital inspection of the gastric mucosa by nonoperative means and points out its clinical advantages over other well established methods. The history of gastroscopy clearly shows that the development of the flexible gastroscope has led to its use as a routine in many of the hospital clinics abroad and that it is rapidly coming into favor in this country. The new instrument and its method of introduction are well described and illustrated. The technic of its passage is comparatively simple, and gastroscopy is now readily performed in the outpatient clinic. The number of contraindications to this form of examination are small, with disease of the esophagus standing out as the chief obstacle to the procedure. The clinical results are given in some detail. Although the evidence obtained is subject to errors of individual interpretation, it may be of definite diagnostic and therapeutic value in a number of diseases of the stomach. To epitomize the clinical potentialities of this objective method in comparison with roentgenographic studies, it may be said that gastroscopy is superior when the pathologic process is widespread and superficial and that roentgen examination is superior when well localized, pronounced lesions are present. Gastroscopic examination should precede an operation on the stomach. Its scientific potentialities are great, as it is adding much useful information regarding the progress in treatment and classification of intragastric disease.

The use of the flexible gastroscope is well exemplified by Carey.[7] He records a number of instances in which the gastroscopic findings indicated the correct diagnosis when other methods of examination either revealed no abnormality or were in error. It is particularly important to prove the presence of gastritis if it is suspected either alone or in conjunction with some other lesion of the stomach or of the duodenum.

"The introduction of gastroscopy into the field of diagnosis and research marks one of the truly great advances in the realm of gastroenterology," Boros states.[8] His observations are based on 100 cases, and in only 6 of these was the procedure unsuccessful. He has found that the quantity of gastric juice secreted in response to a test breakfast has no relation to the occurrence of inflammatory manifestations in the gastric mucosa. The presence or absence of gastric acidity does not in itself predicate the existence of inflammation, and normal acidity may be present in a diseased stomach. He has found by endoscopic means that there are marked gastric changes in diseases affecting the biliary tract and that the diagnosis of gastritis belongs entirely within the realm

6. Schloss, J.: Gastroscopy, Internat. Clin. **4**:1, 1936.

7. Carey, J. B.: The Use of the Flexible Gastroscope, Minnesota Med. **19**:652, 1936.

8. Boros, E.: Gastroscopy: Observation in One Hundred Cases, Am. J. Digest. Dis. & Nutrition **3**:533, 1936.

of the gastroscope. Gastroscopy's applicability includes the group of cases in which the diagnosis is obscure and further investigation is indicated.

In an article entitled "Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach: The Musculus Sphincter Antri; Observation of the Position of the Stomach; the Mucosal Folds," Schindler[9] compares his gastroscopic findings with those of the anatomist, the physiologist and the roentgenologist. Many of his findings do not coincide with those obtained by other methods. Any physician proposing to use a gastroscope should read this article in its entirety.

The gastroscopic findings in grave vomiting of pregnancy seem to explain adequately the mechanism of this troublesome condition. Chevallier and Pigeaud[10] have long recognized that this type of vomiting is accompanied with pronounced blanching of the gastric mucosa. Recently in 3 cases they were also able to make out that there is pronounced atony of the gastric fundus, with persistent hypertonicity and spasm of the pyloric sphincter and the pylorus muscle. The spasm may be permanent during the period of observation, or there may be occasional brief periods of relaxation. These observations adequately explain why neither liquids nor solids can be maintained in the stomach and why the introduction of a tube into the duodenum is so important in the treatment of vomiting of pregnancy.

The value of gastroscopy in correlating the presence of gastritis in a number of disorders of the skin and its etiologic relationship with these disorders is well borne out in a series of three reports by Chevallier and Moutier.[11] They emphasize the importance of subjecting a patient with chronic urticaria, eczema or one of certain other dermatoses to direct observation of the gastric mucosa by means of the gastroscope.

Phytobezoars are rare, but the roentgenographic appearance of the tumor in the stomach is usually characteristic. Moersch and Walters[12] report the first case of this condition in which the bezoar has been visualized and recognized preoperatively by means of gastroscopy. Gastric symptoms followed a persimmon "spree," and ultimately gastrotomy revealed a rocklike tumor, approximately 7.5 by 10 cm. Direct gastroscopic observation of the tumor may be of value as an added diagnostic procedure.

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9. Schindler, R.: Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach: The Musculus Sphincter Antri; Observations of the Position of the Stomach; the Mucosal Folds, Am. J. Digest. Dis. & Nutrition **3**:149, 1936.

10. Chevallier, R., and Pigeaud, H.: Les renseignements fournis par la gastroscopie dans les vomissements graves de la gestation, Lyon méd. **157**:562, 1936.

11. Chevallier, P., and Moutier, F.: L'estomac des eczémateux, Arch. d. mal. de l'app. digestif **26**:75, 1936; L'estomac des urticariens, ibid. **26**:83, 1936; Les localisations gastriques spécifiques des dermatoses, ibid. **26**:87, 1936.

12. Moersch, H. J., and Walters, W.: Phytobezoar with Visualization by Means of Gastroscopy, Am. J. Digest. Dis. & Nutrition **3**:15, 1936.

The relation of gastritis to the formation of peptic ulcers has attracted wide attention. One school of thought claims that gastritis leads to ulceration and that the two conditions are essentially the same disease. The other school claims that they are independent diseases. Chevallier [13] is of the latter school and relies on gastroscopy to prove his contention. He reports 2 cases of gastric ulcer, giving illustrations of the endoscopic findings and also of the resected specimens. In 1 case there was periulcerous gastritis, but in the other no gastritis existed. Gastroscopic examination should precede operation for peptic ulcer to determine the extent of gastritis, if present, as a wider dissection is indicated when there is a surrounding area of localized inflammation.

The pyloric obstruction observed in adults who are free from peptic ulcer and from carcinoma is usually considered to be due to benign hypertrophy of the pyloric musculature. That this is not always true is clearly brought out in a case reported by Chevallier,[14] in which gastroscopy supplied important diagnostic information which has heretofore been lacking when this problem has been encountered. The patient had pernicious anemia of severe degree. Gastroscopy revealed diffuse atrophy of the mucosa of the body of the stomach and diffuse tumefying edema of all the mucosa of the pyloric region. Subsequent roentgen examination revealed the amputation of the pyloric antrum that is usually considered typical of a gastric malignant growth. The anemia cleared up with liver therapy, and the pseudocancerous tumor disappeared completely. Without surgical exploration the exact knowledge of the nature of this phantom tumor could be obtained only by its direct inspection through the gastroscope.

Another somewhat similar case is reported by Cordier and Chevallier.[15] In this instance there was a transient tumor of the pylorus, which appeared and disappeared and when present gave roentgen findings suggesting a neoplasm. Gastroscopy revealed the true nature of this condition. There was an area of sharply localized edema of the mucosa of the pyloric region, reaching its maximum median to the anterior pillar and thereby completely obscuring the pyloric orifice. The rest of the gastric mucosa was free from abnormal changes. Apparently this phantom tumor may be classed as an allergic phenomenon similar to the recurrent localized forms of edema described by Quincke. The presence of these mucosal lesions has often been suspected in the group of conditions described as visceral erythema, and direct observation of the

13. Chevallier, R.: La gastrite péri-ulcéreuse, J. de méd. de Lyon **17**:73, 1936.

14. Chevallier, R.: Un nouveau cas de pseudo-cancer pylorique au cours d'une anémie de Biermer; diagnostic gastroscopique, Lyon méd. **157**:218, 1936.

15. Cordier, V., and Chevallier, R.: Un cas d'oedème fugace antro-pylorique pseudo-tumoral; aspects radiographiques et gastroscopiques, Lyon méd. **157**:384, 1936.

gastric mucosa through the gastroscope now makes possible the verification of these suspicions, at least as far as the stomach may be involved.

Benedict,[16] of Boston, has had wide experience in studying gastric cancer through the gastroscope. He observes that gastroscopy is important in selected cases of neoplasm of the stomach in order to make possible the early diagnosis of carcinoma of the stomach, in differentiating benign from malignant lesions, in determining the location and extent of the lesion and in excluding intragastric pathologic conditions. Pratt [17] urges the use of the gastroscope in conjunction with the Gruskin test to further earlier diagnosis of cancer of the stomach. An important use of gastroscopy is to follow the effect of treatment on gastric lesions. Arloing, Morel, Josserand and Chevallier [18] report 6 cases of gastric cancer in which they directly observed a diminution in the area of tumor infiltration coincident with intravenous therapy with "ferriscorbones" (combinations of dehydroxycevitamic acid and iron and other metals). The value of their observations lies in the method employed to control their studies rather than in any therapeutic results produced.

Schindler,[19] who more than any other person is responsible for the recent development of gastroscopy and the knowledge of the gastric mucosa accruing thereby, reports on the clinical value of gastroscopic examination of the stomach. The procedure with the flexible gastroscope is simple and safe and permits visualization of the greater part of the stomach. The two real difficulties are, first, orientation in the large gastric cavity and, second, the interpretation of observations. In order to overcome these difficulties one must have an extensive knowledge of the normal gastric mucosa and also a wide experience with all its abnormalities. Slight pathologic changes may be overlooked, which is not of great practical importance, but, worse, perfectly normal variations may be interpreted as the effects of disease. Ulcers of the duodenum and pyloric channel are not visible through the gastroscope, and prepyloric ulcers are rarely, if ever, seen. Pyloric obstruction observed roentgenographically is benign if no tumor mass is directly visible and if the pylorus cannot be observed because of distortion from prepyloric adhesions. Ulcers of the angulus and lesser curvature are generally well seen, although they may not be visualized roentgeno-

16. Benedict, E. B.: Gastroscopic Observations of Neoplasm, New England J. Med. **214**:563, 1936.

17. Pratt, G. H.: Diagnosis of Cancer of the Stomach: The Use of the Gastroscope and the Gruskin Test, Arch. Surg. **33**:138 (July) 1936.

18. Arloing, F.; Morel, A.; Josserand, A., and Chevallier, R.: Action désinfiltrante des injections intra-veineuses de ferriscorbones sur six cas de cancer gastrique sous contrôle du gastroscope, Lyon méd. **157**:333, 1936.

19. Schindler, R.: On the Clinical Value of Gastroscopy, Proc. Staff Meet., Mayo Clin. **2**:747, 1936.

graphically. However, in some cases an ulcer which is readily outlined on roentgen examination cannot be located through the gastroscope. Antrum gastritis, which is said to accompany peptic ulcer, has not been observed; hypertrophic ulcerative gastritis of the body of the stomach is frequent. Superficial gastritis is common, but ordinarily it heals. It may develop into chronic atrophic gastritis, usually with anacidity. A completely atrophic gastric mucosa may regenerate with liver therapy. Chronic hypertrophic gastritis is an important clinical entity in which healing does not occur. It is found around gastric ulcers. Chronic gastritis is the most common postoperative disease of the stomach and is severe. The diagnosis of a localized carcinoma may be made by a glance at the gastric wall. A number of patients for whom the diagnosis was made early have survived operations for three, five or even ten years. The operability of gastric carcinoma can be decided on by gastroscopy and gastroscopy alone, and only when the condition is known to be operable should surgical intervention be employed. It is suggested that each patient with atrophic gastritis or with a benign epithelial tumor, both forerunners of carcinoma, should be examined twice yearly by gastroscopy and the roentgen relief method.

The development of the flexible gastroscope has led to its use in intragastric photography. Goyena, Islenghi and Hofmann,[20] of Argentina, review the development of this subject and describe in detail the gastrophotor of Heilpern. This flexible photographic unit carries two cameras capable of taking sixteen simultaneous exposures of the gastric mucosa. Changing the position of the gastrophotor makes possible a practically complete photographic record of the mucosa of the entire stomach. The position of the unit is controlled by fluoroscopic examination. When this is satisfactory the stomach is dilated with air. Then automatically the objectives of the cameras are uncovered, and at the same time the electrical contact is made, giving an intense intragastric illumination. The exposures occur just at the time the walls of the stomach are about to contract. In this gastrophotor the difficulties of the older forms of apparatus are apparently overcome. The instrument can be passed easily and safely, and complete permanent records can be obtained of gastric lesions.

GASTRITIS

Until recently the diagnosis of gastritis was all too often a cloak for ignorance. It was used to cover almost any type of acute or chronic indigestion when the cause of the symptoms was obscure. When the diagnosis was correct it was based rather on inference than on fact. The glib pronouncement of yesterday that a patient was suffering from gastritis is in the same category with the oft repeated diagnosis of

20. Goyena, J. R.: Islenghi, J. P., and Hofmann, H.: Gastrophotography. Rev. Gastroenterol. **3**:158, 1936.

"intestinal influenza" of today. With the advent of improved histologic studies of the gastric mucosa and particularly with the advent of the flexible gastroscope, gastritis is gradually being brought out into the light and is better understood today than ever before. The advancement in knowledge of this condition and how much yet remains which is ill understood may be judged from the following abstracts:

Schindler and Ortmayer [21] present their classification of chronic gastritis, based on 1,200 gastroscopic examinations. The histologic methods leading to an anatomic classification are unsatisfactory, owing to a lack of knowledge of the effect of ligatures on the vessels when specimens of gastric tissue are obtained by surgical resection. Three forms of gastritis—the hypertrophic, the atrophic and the mixed—have been clearly demarcated by the pathologist; but it is not proved that they cannot appear in an otherwise normal stomach. Also, these findings frequently are present in a patient without any gastric symptoms. The authors prefer to consider that the mucous membrane of the adult who has no symptoms is normal.

Gastroscopic examination is a direct method of examining the gastric mucous membrane. Even the deeper-lying lesions can be observed, as the mucosa is transparent. Gastritis is characterized by changes associated with swelling, exudation or atrophy, although atrophy may be degenerative, as in pernicious anemia. Observations have been made in 346 cases of the chronic form of gastritis. About 50 per cent of the gastroscopic studies show these changes. Chronic benign ulcer is not included in the description of chronic gastritis. Repeated observations in the same case are essential to an understanding of the course of gastritis and are essential to correct classification. Four types of gastritis are recognized by the direct method of examination: (1) superficial, (2) atrophic, (3) hypertrophic and (4) that following operations on the stomach. They differ as to gastroscopic picture, course and prognosis.

In superficial gastritis the surface epithelium is cloudy and may be spotted, edematous, superficially eroded and slightly hemorrhagic. Adherent glairy secretion is a feature. These changes are most marked in the body of the stomach and usually are absent from the antrum. With careful control of the diet and lavage this disease disappears completely. In atrophic gastritis the mucous membrane loses its normal orange-red color and becomes gray and transparent; the underlying blood vessels may be visible. This condition usually remains stationary but may rarely develop into diffuse general atrophy. Normalcy is not regained, but the patient suffers little. The superficial form may develop into the atrophic, and this can occur rapidly. In hypertrophic gastritis

21. Schindler, R., and Ortmayer, M.: Classification of Chronic Gastritis with Special Reference to the Gastroscopic Method, Arch. Int. Med. **57**:959 (May) 1936.

the chief finding is swelling of the mucosa, which may result in pseudopolyposis. Hemorrhage is often extreme, multiple erosions come and go and ulceration may occur. All these changes are much more frequent in the corpus than in the antrum. The term gastritis chronica hypertrophicans ulcerosa is applicable. None of the author's patients with this serious disease have regained complete health, but atrophic gastritis develops rarely. In postoperative gastritis the prognosis is poor, as in even the superficial forms there is no tendency to heal. An etiologic classification of gastritis, although desirable, is not at present possible, owing to a lack of knowledge of the causes. Symptoms, laboratory findings and roentgen observations may be helpful but are of little or no diagnostic value compared with gastroscopic observations, particularly serial observations.

At the Brussels International Congress for Gastro-Enterology, Zweig,[22] of Vienna, reviewed completely the present status of chronic gastritis. In his opinion medical interest in peptic ulcer and functional disturbances of the stomach had almost submerged the clinical diagnosis of chronic gastritis until most recently. The classification of exogenous and endogenous gastritis is still serviceable. Gastritis and ulcer are always associated, although their causal relationship is as yet undetermined. Many authors believe that the incidence of gastritis in adults with ulcer is 100 per cent. It reaches a peak in patients between 40 and 50 years of age and falls off markedly in older patients. Symptomatically low or no acidity and excess of mucus are the important symptoms, combined with the gastroscopic picture of chronic catarrh and hypertrophy or atrophy of the gastric mucosa. Roentgen findings are valuable. Treatment consists of (1) a bland diet; (2) medications, the nature of which vary with the presence or absence of free acidity; (3) local treatment, such as irrigations; (4) *Trinkkuren*—the ingestion of large amounts of alkaline waters, and (5) surgical treatment in cases of severe and intractable gastritis.

Mahlo [23] presents some original ideas on the relationship between the formation of gastritis and the gastric mucus. The mucus has many important functions, such as protection of the mucosa, absorption of hydrochloric acid to counteract alkalis and ferments, reactivation of ferments and protection of vitamin C. It is a complex substance composed of albumin, carbohydrate and mucosulfuric acid. It has the function both of absorbing and of chemically binding hydrochloric acid. Injurious alterations in the mucus may be brought about both by an effect on the secreted mucus and by injury to the mucus-secreting cells. The commonest cause of gastritis is alcohol, which produces more or less

22. Zweig, W.: Die chronische Gastritis, Wien. klin. Wchnschr. **48**:1535, 1935.

23. Mahlo, A.: Beziehungen zwischen der Entstehung der Gastritis und dem Magenschleim, Deutsche med. Wchnschr. **62**:1216, 1936.

marked changes in the mucus, depending on its concentration. The absorptive capacity of the mucus is interfered with, and histamine is set free, influencing the production of hydrochloric acid and water. A failure of mucus protection to mucosal epithelium results and vasodilatation occurs. A peptic ulcer may arise in such an area of localized gastritis. The "vital resistance" of the tissues often prevents this sequence of events.

Other common exogenous causes of gastritis are acetylsalicylic acid and nicotine. With normal values for acid in the stomach, the mucus will have maximum absorption of hydrochloric acid, and none of the acetylsalicylic acid will be absorbed. Absorption will take place in case of subacidity or anacidity, and irritation of the gastric epithelium will result. Nicotine is not absorbed by either acid or alkaline gastric mucus and cannot have a direct effect on the lining epithelium of the stomach. It is absorbed in other organs and exerts its effect in the stomach through the splanchnic nervous system. The localized gastritis accompanying gastric carcinoma, the author believes, is due to the action of a special ferment selective for epithelial tissues. The protective mechanism is increased production of mucus. The author states that he once inadvertently swallowed some of this ferment, causing gastritis for three weeks; and although he had never had any gastric disturbance previously, he has had distress occasionally ever since this unfortunate episode. It is evident that localized gastritis, like ulcers, has no single cause.

Although in gastritis there is characteristically an excess secretion of mucus, when ulcers are present there is often less mucus than normally, so that the lesion is not well protected. Injections of histidine may be beneficial in this type of disorder by increasing the production of mucus. As mucus is digested in the duodenum and amino-acids, such as histidine, are set free, a diminished production of mucus means a diminished production of histidine. The beneficial effects of mucin administered orally or of histidine administered parenterally may be due to the greater quantity of histidine introduced, making possible an increased secretion of mucus. Clinical experience supports these suppositions.

Darling [24] presents a compact and up-to-date review of chronic gastritis in the *Medical Journal of Australia.* He emphasizes that achlorhydria may be only symptomatic and may exist without any anatomic change in the gastric mucosa. Carnot and Gaehlinger [25] review gastritis in *Paris médical,* emphasizing the greater perfection in diagnostic investigations which exist today.

24. Darling, H. C. R.: Chronic Gastritis, M. J. Australia **2**:45, 1936.

25. Carnot, P., and Gaehlinger, H.: La pathologie digestive en 1936, Paris méd. **1**:273, 1936.

Hurst [26] also reviews the subject of gastritis. He particularly stresses that it is likely to develop in patients with constitutional hyperchlorhydria or with hypochlorhydria or achlorhydria, because of a lack of secretion of protective mucus. It not only predisposes to such intrinsic diseases of the stomach as peptic ulcer and carcinoma but is responsible for such extrinsic disorders as disturbances in hematopoiesis and disorders in the nervous system.

One of the series of articles on treatment in general practice in the *British Medical Journal,* which was written by S. W. Patterson,[27] is on gastritis. As his classification and treatment of this condition are of the old textbook variety, this paper is mentioned only to illustrate how long it takes new and accepted concepts of a disorder to reach the general practitioner. If "faulty table habits" and a "lack in pleasant surroundings" during meals are truly causes of chronic gastritis, as the author states, surely most Americans should suffer from this disease.

Pevsner and Gordon [28] believe that the clinical aspects of chronic gastritis have not been sufficiently studied. On the basis of a detailed study of 500 cases they recognize two general groups: one in which gastritis is a concomitant of some other disease and one which is basically a clinical entity with a definite clinical picture. This picture may vary, depending on whether there is deficient gastric secretion or normal or excessive secretion. Achylia may be responsible for serious manifestations outside the stomach, such as those which occur in some of the anemias and in nutritional allergy. Hypersecretion is associated with neuro-endocrine and psychotic types of disturbances. One type of secretory disturbance may merge into the other, the two being accompanied with similar changes in motility noted roentgenographically. Chemical analysis of gastric secretion and roentgen studies of the gastric mucosa by the relief method give accurate information as to the course of the inflammatory lesion. Dietary treatment is the fundamental form of therapy in chronic gastritis and must vary with the amount of gastric secretion and the degree of inflammation. The neurohumoral influence must be taken into consideration.

Eusterman [29] discusses the problem of gastritis and reports 10 histologically verified cases. Although only two serious diseases of the stomach—cancer and peptic ulcer—are usually considered in cases in which gastric disorders are manifest and although healthy skepticism has been maintained toward gastritis, this disorder must now be con-

26. Hurst, A. F.: Gastritis, Arch. f. Verdauungskr. **58**:121, 1935.

27. Patterson, S. W.: Treatment of Acute and Chronic Gastritis, Brit. M. J. **1**:272, 1936.

28. Pevsner, M., and Gordon, O.: Clinique et diétothérapie des gastrites chroniques, Acta med. Scandinav. **88**:278, 1936.

29. Eusterman, G. B.: The Gastritis Problem: Notes on Histologically Verified Cases, South. M. J. **29**:684, 1936.

sidered of frequent occurrence. Inflammation commonly causes symptoms in many other organs, and it should not be surprising that recent investigations prove this to be true in the stomach. However, there is no close correlation between the symptoms and the presence or degree of inflammation. Furthermore, the impression is given that the enthusiastic gastroscopist finds some abnormality of the gastric mucosa in the majority of cases. The diagnosis must be guarded as to the relation of gastritis and the patient's complaint, and pathologic confirmation is of the utmost value. Classification, symptomatology and treatment are dealt with in some detail.

After a description of the histologic picture of the normal gastric mucosa, Baker,[30] of the Mayo Clinic, describes the changes occurring in chronic gastritis. Part or all of the mucosa may be involved. In cases of not far advanced gastritis there is observed an increase in stroma tissue and in lymphocytes which may form germinal centers. In cases of more advanced gastritis, atrophy of the specific epithelial cells occurs, hyperplasia may take place or these cells may present the picture of intestinal epithelium. The muscularis mucosae is always involved, with thickening due to both hypertrophy and fibrosis of the muscle tissue. Erosion or ulceration of the mucosa may take place.

Konjetzny [31] believes that the diagnosis of gastroduodenitis is based on a definite pathologic picture with clearcut clinical findings. Histologic studies prove that there is acute and more or less pronounced erosive gastroduodenitis when the "ulcer syndrome" is noted but no ulcer is present. The pyloric syndrome, pyloritis, pylorospasm, hyperesthesia of the stomach and irritability of the stomach are less exact terms for the same pathologic condition. On purely clinical grounds it is not possible to differentiate between gastroduodenitis and gastric and duodenal ulcers. Treatment belongs to the realm of internal medicine and not of surgery. Even organic pyloric stenosis is often due to edema associated with the inflammation, and improvement can readily be demonstrated roentgenographically from eight to ten days after the start of dietary, anticatarrhal and atropine treatment. Surgical treatment is to be deplored under these circumstances. Hypertrophic pyloric stenosis and pyloric carcinoma must not be confused with gastroduodenitis, as their treatment is operative.

Swalm, Jackson and Morrison,[32] of Philadelphia, have attempted to correlate the clinical and gastroscopic findings in a series of cases of

30. Baker, C. P.: Histopathology of Chronic Gastritis, Proc. Staff Meet., Mayo Clin. **11**:521, 1936.

31. Konjetzny, G. E.: Das Krankheitsbild der Gastro-Duodenitis, Med. Klin. **32**:473, 1936.

32. Swalm, W. A.; Jackson, C., and Morrison, I.: Correlation of Clinical and Gastroscopic Findings in Chronic Gastritis with Report of Cases, Rev. Gastroenterol. **3**:219, 1936.

chronic gastritis. They point out that there is no definite correlation between histologic abnormalities of the gastric mucosa and disturbances of gastric secretion, although at times hyperacidity may be associated with antral gastritis and subacidity with fundal gastritis. However, changes in secretion are often dependent on variations in the function of the nervous system. The important point of the relation of gastritis to peptic ulcer seems to have been cleared up by accurate histologic studies and by skilled gastroscopic observations. Gastritis almost invariably accompanies ulceration. The cytologic study of the gastric sediment should not be neglected, as it is a valuable index of inflammatory changes.

These authors carried out gastroscopic examination 196 times in 135 cases, and gastritis of various types was revealed in 35 per cent of the cases. Their criteria for diagnosis are recorded in detail. In 9 of 10 cases of peptic ulcer there was definite gastritis. In all but 1 of 13 cases of hypertrophic gastritis there was normal or high acidity, and in this 1 case the condition was associated with a gastric malignant growth. In all 9 of the cases of atrophic gastritis there was low or no acidity. In other mixed groups there were no constant secretory changes. It is evident that proliferative hypertrophic gastritis may be the forerunner of peptic ulcer, as its association with hyperchlorhydria is the usual finding. Seven cases of hypochromic achlorhydric anemia are described, atrophic gastritis being present in each case.

These authors have not found roentgenographic relief study of the mucosal pattern to be an aid in the diagnosis of gastritis when checked by gastroscopic studies, and they feel that many conditions clinically suggesting peptic ulcer are really gastroduodenitis.

Leotta,[33] of the University of Palermo, feels that gastritis occurs in all sorts of intra-abdominal diseases, not alone with peptic ulcer or cancer of the stomach. It is a predecessor of gastroduodenal ulcer, but there is no sharp dividing line between chronic gastritis without ulceration and that with ulceration. In the latter type the inflammation is prolonged, with marked formation of scar tissue. A case of localized hypertrophic gastritis is reported from Brazil by Cotrim.[34] Clinically and roentgenologically the condition appeared to be gastric carcinoma, but operation disclosed a benign lesion of an inflammatory nature.

Despite the extensive studies of gastric physiology during the last century, knowledge of gastric functions is far from complete. However, a new doctrine has recently come to light: that the stomach occupies a

33. Leotta, N.: Gastrite cronica ed ulcera gastro-duodenale, Riforma med. **51**:1823, 1935.

34. Cotrim, E.: A proposito da hypertrophia localizada da mucosa gastrica simulando carcinoma, Ann. paulist. de med. e cir. **31**:501, 1936.

place of prime importance in functions of the blood. Guillaume [35] notes that in addition to the well known external gastric secretions and the pyloric hormonal secretion stimulating the glands of the fundus, there is also a hormonal principle regulating hematopoiesis. This substance is found in the liver and is deficient in severe hepatic disease, such as advanced cirrhosis or acute yellow atrophy. It is not a product of the hepatic parenchyma but is stored there, awaiting the demands of the blood-forming organs. In the absence of this hormone, the production of blood cells returns to the embryonal type, and pernicious anemia results. Achylia is the rule in this form of anemia, and the basis of its development is degenerative gastritis, which is frequently accompanied with stomatitis, glossitis and intestinal disturbances.

Gastritis with achlorhydria or hypochlorhydria is also associated with hypochromic microcytic anemia, which may be considered the inverse of pernicious anemia. Diffuse atrophic gastritis is constantly observed gastroscopically in the course of this type of anemia and may be present in the nonanemic stages. The presence of glossitis simply indicates that there is gastritis. Histologically, the gastric mucosa may be purely atrophic or may show hypertrophic atrophy. It is probable that achylia, atrophy and anemia are coordinate and dependent manifestations, but it is as yet difficult to correlate clinical symptoms with them as they are so often symptomless in themselves. Certainly they frequently occur without an absence of the hormonal secretion stimulating hematopoiesis.

A group of French investigators [36] have studied the relation of atrophic gastritis to the course of alcoholic polyneuritis and have considered the clinical, chemical and gastroscopic aspects of this problem in 50 cases. Dyspeptic symptoms are constant and precede those of involvement of the nervous system by weeks or even months. In 33 cases achlorhydria occurred after the injection of histamine, and hypochlorhydria was marked in 12 cases. Early in the course of the disorder gastroscopy showed atrophic gastritis, and when the gastric mucosa was observed during the first two months and before the onset of the neuritis, gastritis was a constant finding. However, later, although the evidence of neuritis persisted, gastroscopic examination might show a normal picture. It is evident that gastric inflammation precedes the development of the neural lesions and may clear up before those lesions do.

In a discussion of precancerous gastritis Moutier [37] states that gastritis does not produce cancer but provides the soil on which cancer

35. Guillaume, A. C.: Etude physiopathologique sur le rôle hématopoiétique de l'estomac, Arch. d. mal. de l'app. digestif **26**:241, 1936.

36. Villaret, M.; Moutier, F.; Justin-Besançon, L., and Klotz, H. P.: Caractère spécial des troubles gastriques au cours de la polynévrite alcoolique, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:1155, 1936.

37. Moutier, F.: La gastrite précancéreuse, Paris méd. **1**:283, 1936.

develops. Peptic ulcers associated with gastritis are not concentrated anatomically in the same areas in which cancer develops and are not a cause in themselves of cancer. The clinical courses of gastritis and early carcinoma of the stomach may merge, making any definite differentiation impossible. Apogastritis, gastritis accompanied with manifestations elsewhere in the body, for instance, in the skin, blood or nervous system, does not produce an increased incidence of gastric malignant disorders, nor do the disorders associated with various forms of anemia. Ignorance of the nature of cancer is still too great to permit relating the cause directly to gastritis.

The relation of gastritis to carcinoma of the stomach has been analyzed from pathologic material by Tuomikoski.[38] In a study of 158 resected specimens he noted pangastritis in 77 per cent, antral gastritis in 22 per cent and no gastritis in only 2 cases. That atrophic gastritis is the primary predisposing disease is indicated by the following facts: 1. The localized and generalized forms are morphologically similar. 2. The characteristic changes of chronic gastritis are no more marked near the tumor than at a distance from it. 3. The incidence and intensity of these changes are independent of the nature of the tumor. 4. There is evidence that the changes in the gastric mucosa have taken a long time to develop. The author concludes that in most cases gastric carcinoma probably arises on a basis of chronic atrophic gastritis.

Attention is called to the association of gastritis with urticaria by Chevallier and Moutier.[39] They studied 24 cases of urticaria relative to the digestive origin of the disorder. They made a gastroscopic examination in 20 cases, and the diagnosis of gastritis was established on the gastroscopic evidence. In half the cases there was gastritis, which was of the atrophic variety in 8 instances. The majority of the patients had achlorhydria. While it is evident that the cause of urticaria is not necessarily directly digestive in origin, they feel that atrophic gastritis with achlorhydria was the rule in too large a group of cases to be coincidental. The importance of this association was strengthened by the fact that in 8 cases the condition was greatly improved or cleared up entirely when large doses of iron were given, while 4 patients with normal gastric mucosa and normal gastric secretion failed to respond to iron. An analogy exists between the excellent response of patients with chlorotic anemia and atrophic gastritis and that of patients with chronic urticaria and the same gastric defect. Certain French authors[40] report on a carefully studied case of gastritis with

38. Tuomikoski, V.: Gastritis and Carcinoma, Acta chir. Scandinav. **78**: 251, 1936.

39. Chevallier, P., and Moutier, F.: Les urticaires avec gastrite atrophique, Ann. de dermat. et syph. **7**:337, 1936.

40. Gaté, J.; Thiers, H.; Chevallier, R., and Michell, P. J.: A propos des modifications gastriques dans l'eczéma, Lyon méd. **158**:130, 1936.

achlorhydria and erythrodermic eczema. The cutaneous lesions were unaffected by a number of treatments until iron was administered, when they markedly improved and pruritus disappeared.

Gastritis has been described in rats fed a diet deficient in vitamin B_1. Hemorrhagic erosions and chronic ulcers are also said to occur. Simpson,[41] not satisfied with the methods employed in producing these lesions, carried out similar experiments in which he rapidly excluded vitamin B_1 from the diet. Certain microscopic changes developed deep in the gastric mucosa, but there was no evidence of atrophic erosions or ulcerations. These changes following complete deprivation of vitamin B_1 can be of little if any importance in the genesis of gastric ulcer.

HISTIDINE TREATMENT OF PEPTIC ULCER

No new form of therapy in the last decade has received such universal attention and enthusiastic acclaim as the histidine treatment of peptic ulcer. A survey of the current literature makes the reasons for this obvious but also shows the gradual development of a healthy skepticism not only concerning the alleged brilliant results of the treatment but as to the soundness of the few basic experiments which have led to the erection of this therapeutic colossus. Only time and conservative judgment can determine the place that injections of histidine will ultimately occupy in the list of procedures available to combat a disease which has long withstood all panaceas.

A single enthusiastic report of a case by Davis,[42] of Australia, illustrates the remarkably early improvement which may occur in some persons with chronic duodenal ulcer while receiving histamine therapy. In less than three weeks Davis' patient not only was entirely relieved of symptoms but was able to partake of "cold collation, salad, trifle with alcohol in it, and other sweets, and he crowned his indulgence with a large glass of beer and a good nobbler of whisky" without suffering any ill effects. In a careful study of 3 cases Finnegan and Elward [43] noted marked clinical improvement in each. All symptoms, including pain, completely disappeared by the third day of treatment, and the patients were able to return to their usual mixed meat and vegetable diet. Mastronardi and Bagnasco [44] report 12 cases from the Argentine. In 9 not only did pain cease, but there was a satisfactory improvement in

41. Simpson, C. K.: Observations upon Gastritis, Guy's Hosp. Rep. **86**:120, 1936.

42. Davis, K. J. B.: Treatment of Chronic Duodenal Ulcer with Histidine, M. J. Australia **1**:172, 1936.

43. Finnegan, J. F., and Elward, J. F.: Histidine Treatment of Peptic Ulcer: Report of Three Cases, M. Ann. District of Columbia **5**:135, 1936.

44. Mastronardi, V., and Bagnasco, F.: Contribución al estudio applicación de la histidina en las úlceras gastro-duodenales, Rev. Asoc. méd. argent. **50**:955, 1936.

weight and in the number of red blood cells. The course of injections was repeated in 7 instances in an effort to avoid recurrences. Eighteen cases of uncomplicated peptic ulcer treated with histidine are reported from London by Love.[45] Complete relief and disappearance of roentgen evidence of ulceration were obtained in half the cases.

Voigt [46] notes that the efficacy of a form of therapy may be better judged from a few carefully described observations than from statistics. He reports 2 cases of gastric ulcer, including roentgenograms, which illustrate the remarkable healing effect occurring during treatment with histidine. In both cases the ulcers were very large and penetrating, and in both cases they healed completely, although lesions of this type rarely respond to the usual forms of therapy. The author believes the treatment in these 2 cases was a crucial test for treatment with histidine and that the biologic value of the therapy is proved. In a brief review in the *Gazette des hôpitaux* recommending the use of histidine in the treatment of gastroduodenal ulcers, Quénée [47] advises follow-up therapy of two series of six daily injections a year. In this way the impositions of a strict diet may be avoided.

As a follow-up study of a previously reported series of 21 cases, Valini and McLaughlin [48] publish their findings in 73 cases of peptic ulcer in which the patients were treated with histidine and observed over a period of six months. The patients were ambulatory, usually were on a liberal diet and were not given alkalis. Seven of them suffered from gastric ulcers; the rest, from duodenal ulcers. For ten days they received daily intramuscular injections of 5 cc. of a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. If the symptoms were not relieved by then, from two to four times the dose was given daily. The length of the daily treatment varied from ten to sixty days, depending on how soon the alleviation of symptoms occurred; then one or two injections a week for one or two months more were deemed advisable. The authors suggest no indications for the necessity of repeating a course of treatment. These injections were without danger to the patient. Gastric analysis showed a tendency of acidity to be reduced to normal. In 80 per cent of the cases the patient gained weight. The immediate results as to subjective complaints showed complete relief after twenty-four injections in all but 14 cases, and in 3 of these subsequently there was entire relief. This group included

45. Love, R. J. M.: Histidine Treatment of Peptic Ulcer, Brit. M. J. **1**:582, 1936.

46. Voigt, W.: Ueber Erfolge mit der Histidinbehandlung der Ulkuskrankheit, Deutsche med. Wchnschr. **62**:1218, 1936.

47. Quénée, N.: Un traitement classique des ulcères gastroduodénaux: l'histidine, Gaz. d. hôp. **109**:668, 1936.

48. Valini, I. F., and McLaughlin, R. F.: The Histidine Monohydrochloride Therapy of Gastroduodenal Ulcer, Illinois M. J. **69**:39, 1936.

6 of 7 cases of gastric ulcer. All disappearance of the roentgenographic evidence of ulceration occurred in only 37 per cent. One patient with a previously intractable duodenal ulcer was completely relieved by the injections, but perforation occurred two weeks later. (I have had a similar experience.) The authors make the observation that patients with syphilis do not respond well to this form of treatment. They conclude: "This amino acid treatment in our series, as far as the time-factor permits of comparison, has proved much more satisfactory than the various modes of accepted ulcer therapy."

The problem of the effect of histidine on the healing of peptic ulcers has been approached in a direct way by Korbsch.[49] With an experience based on gastroscopy performed about 5,000 times, he has applied the knowledge thus obtained to observing the changes occurring in ulcerating lesions of the gastric mucosa during and after injections of solution of levohistidine monohydrochloride. Serial observations in about 30 cases have enabled him to draw certain conclusions which are well substantiated by thirty-six sketches of the lesions. His conception of the development and course of peptic ulcer must be understood before the results of the studies are considered.

Korbsch states that in his observation of hundreds of ulcers, gastritis has never been lacking and that it is the conditioning process which permits ulceration to appear. Also, the resistance of the gastric mucosa is dependent on vitamins, and if there is vitamin deficiency, gastritis and ulceration will occur. In some instances only the administration of vitamins will restore the stomach to normalcy. Three types or stages of ulceration are observed, and they have a direct bearing on the roentgen findings and response to treatment. The flat ulcer of the mucous membrane gives no positive roentgen signs and tends either to heal spontaneously or to respond rapidly to a diet rich in vitamins. Deeper penetration of such an ulcer, with the development of indurated edges, involves the underlying nerve plexus, causing localized paralysis of the wall of the stomach and an outpocketing of the wall, recognized roentgenographically as the characteristic ulcer niche. The functional paralysis causing the appearance of the niche may quickly clear up under suitable therapy, with early disappearance of the deformity, or it may last for months. In the third stage the development of scar tissue with callus formation greatly delays healing but does not necessarily prevent it. In this stage the niche tends to persist much longer.

Case histories are presented as well as a series of serial drawings of ulcers illustrating their healing to demonstrate the excellent response of ulcers to histidine and to correlate the stages of the ulcer process not only in the therapeutic successes but in the failures. Histidine

49. Korbsch, R.: Ueber den Heilungsmechanismus des Larostidin bei Geschwüren und bei Entzündungen des Magen: ein gastroskopischer Bericht, Arch. f. Verdauungskr. **59**:82, 1936.

promotes healing of the ulcerating process in all stages, but in those instances in which there is a great lack of resistance of the gastric mucosa (vitamin lack), it alone may be without results. Mechanical conditions due to the formation of scar tissue also cannot be entirely remedied by injections of histidine. This form of medication is effective in a number of ways. An increased blood supply to the gastric mucosa can be readily noted through the gastroscope and also an increased tonicity of the whole wall of the stomach. The latter effect will lead to rapid disappearance of the gastric niche when it is on a paralytic basis. An increased flow of mucus is often noted. Indirectly, with the increase in appetite there is an increased intake of food, including the highly beneficial vitamins.

The author feels that repeated gastroscopic examinations give a much better idea of the progress of an ulcer coincident with histidine therapy than alleviation of symptoms or repeated roentgen examinations. He concludes that histidine is a most important *addition* to the therapy of peptic ulcer and that not only may symptoms be rapidly relieved but healing of the ulcer and of the associated gastritis may be markedly stimulated.

Gardiner [50] reports his results in a small number of cases of gastric and duodenal ulcer treated with histidine. His 12 patients were ambulatory although hospitalized; they were not on a restricted diet and received alkalis only in the beginning for postprandial pain. They received twenty-five daily injections each and were subjected to gastric analysis and roentgen studies both before and after treatment. Symptomatic relief was obtained in all the patients, and there was an invariable fall in the gastric acidity. A third of 9 patients followed for from four to six months showed a return of symptoms. It is pointed out that this form of therapy is not a cure but offers an economic saving both to the patient and to the community.

Another small series of cases is reported by Weigand.[51] The usual histidine treatment was given, and most of the patients were relieved symptomatically. No marked changes in acidity were noted. Because prompt symptomatic relief is afforded, follow-up roentgen studies are important, as the organic defect frequently persists. The author's case reports emphasize this.

No evaluation of histidine therapy can be based on Behneman's [52] report on 17 patients with peptic ulcer, all of whom became free from symptoms and one half of whom soon lost the roentgen signs of ulcera-

50. Gardiner, R. H.: Histidine in the Treatment of Gastric and Duodenal Ulcer, Lancet **1**:1352, 1936.

51. Weigand, F. A.: Histidine Treatment of Peptic Ulcer, Pennsylvania M. J. **39**:860, 1936.

52. Behneman, H. M. F.: Late Concepts of Peptic Ulcer Etiology and a Preliminary Report of Modern Therapy, Northwest Med. **34**:453, 1935.

tion. He treated his patients not only with daily injections of solution of levohistidine monohydrochloride but with a modified Sippy diet, gastric mucin, belladonna and sedatives. However, such a combined and extensive therapeutic regimen may prove to be a greater aid to the patient than any single form of management.

Sandweiss,[53] after a comprehensive review of the experimental data and clinical studies of others dealing with the effect of injections of histidine on the course of peptic ulcer, reports a carefully controlled series of 68 consecutive cases. Seven criteria for the effect of new therapeutic measures were kept in mind throughout the course of his observations. These have been lost sight of by many physicians who have enthusiastically reported on the problem; so they are enumerated here. They are: 1. How do the results compare with those of the diet-alkali regimen? 2. How many patients who fail to respond to diet-alkali treatment become free from symptoms with the new method? 3. Will patients tolerate a maintenance diet sooner? 4. Is the interval of freedom from symptoms prolonged, and are recurrences prevented? 5. Is gastric acidity affected? 6. What is the effect on the ulcer deformity as seen roentgenographically? 7. Are there untoward reactions?

Sandweiss' method of study was to place 23 patients who could report regularly for treatment on a course of twenty-four daily injections of histidine; the 46 who could not report regularly were started on the diet-alkali regimen. Persons in one group for whom the treatment failed were then placed on the other form of therapy. Consequently 53 patients were treated with diet and alkalis and 40 with histidine. Those receiving injections were continued on the same diet which they had received previously. Not all of them received a full course of twenty-four injections. The percentage of remissions and the percentage of moderate improvement were practically the same for the two groups; approximately three fourths of all the patients were benefited. In all of the 22 patients who showed remissions while receiving histidine there was a sudden disappearance of discomfort after one or two injections. It was apparent that if a patient was not relieved within the first week he was not likely to be benefited later and that a full course of treatment was no more likely to prevent relapses than a short one, as 10 patients who returned with a recurrence of symptoms of ulcer within three months were among those who received twenty-four consecutive daily injections. The histories are presented of 3 patients in whom symptoms were aggravated by the injections of histidine.

About the same percentage of patients were relieved by injections of histidine when diet had failed as were relieved by diet when histidine failed. Forty-five per cent of the patients treated with histidine were

53. Sandweiss, D. J.: Treatment of Gastroduodenal Ulcer with Histidine Monohydrochloride (Larostidin), J. A. M. A. **106**:1452 (April 25) 1936.

not free from symptoms while taking a maintenance diet. Of particular interest was a recurrence of symptoms in 85 per cent of 20 patients within six months when they were treated by the injection method. A similar comparative follow-up study of 29 patients under diet-alkali management showed recurrences in only 31 per cent. No constant alteration in gastric acidity occurred. None of the 24 patients whose condition was checked by roentgen examination or by operation after histidine treatment showed disappearance of the ulcer. Forty per cent of the patients receiving injections had mild reactions. A preliminary report is included in the treatment of ulcer with daily injections of 5 cc. of distilled water. In 20 patients so treated the favorable results are comparable to those obtained by injections of histidine, 60 per cent obtaining complete relief.

Sandweiss does not feel that there is sufficient experimental evidence that histidine promotes the healing of peptic ulcers or that it prevents their occurrence. From his clinical experience the use of histidine as a routine is not warranted. It should be reserved for trial in treatment of patients who do not respond to diet and alkalis, but only about 50 per cent of these may be expected to become free from symptoms.

Bulmer [54] was one of the first clinicians to report on a large series of patients with peptic ulcer treated with injections of histidine. In 1934 he published the results obtained in 52 patients. He has since treated 74 additional ambulatory patients, making a total of 126 patients, and presents not only the immediate results but, what is more important, a follow-up study of 82 of the patients, the duration of the follow-up period being from four to twenty-five months, with an average of sixteen months. The location of the ulcers was about equally divided between the stomach and the duodenum. The immediate results for the whole series were as follows: Seventy-three per cent of the patients were free from symptoms, 5 per cent were much improved and 22 per cent were unrelieved. The follow-up results for 82 of the 92 patients who were free from symptoms were as follows: Thirty-two per cent were symptom free, and 48 per cent had a relapse. No periodic injections for the prevention of relapses were tried. Bulmer concludes that histidine therapy has as good an effect on ambulatory patients as diet and alkalis but that it should be used not as an alternative but as an adjunct to the usual methods of diet and alkalis. Unfavorable effects included the occurrence of both perforation and severe hemorrhage during the treatment. (I have encountered a number of such "accidents" even in the presence of excellent symptomatic relief.) The disappearance of abnormalities roentgenographically did not necessarily mean that the ulcer had healed. Histidine treatment should be reserved for patients with simple, uncomplicated ulcers, those with "stoma-ulcer" and those for whom the usual methods have failed.

54. Bulmer, E.: Histidine Treatment of Peptic Ulcer, Lancet **2**:734, 1936.

The author offers an interesting comment on supposed human deficiency of histidine as the cause of peptic ulcer. Such a known deficiency occurs only during pregnancy, and he does not recollect ever having noted a case in which peptic ulcer was coincident with pregnancy. Does peptic ulcer occur in pregnancy?

A controlled series of 41 patients with peptic ulcer treated with histidine alone is reported on from New York by Martin.[55] There were 40 patients in the control group on the diet and alkali therapy for ambulatory patients. Seventy-two per cent of the group receiving the injections of histidine were relieved of symptoms, usually between the fifth and the seventh day. Those who showed an ulcer crater roentgenographically at the end of the month were less likely to be free from symptoms than those from whose roentgenograms the crater had disappeared. In 11 patients no crater was demonstrated after this short lapse of time. Thirty-nine patients were followed as long as from six to twelve months later, and 26 had had one or more relapses. Gastric acidity varied somewhat, but no constant trend toward a decrease of acidity was found. Over half the patients gained weight; this was evidently in direct proportion to the relief of symptoms and the resulting increased caloric intake. Six patients with ulcer received six injections daily of saline solution, and 3 of them were relieved of symptoms before injections of histidine could be started. In the control series of patients 78 per cent received symptomatic relief, and late relapses occurred in the usual proportion. The symptomatic and roentgenographic responses of the patients receiving histidine were not quite as good as those of the patients on the diet-alkali regimen. Martin's final conclusion is that "the therapeutic indications for histidine in the treatment of peptic ulcer are necessarily limited. The extravagant claims that have been made for this substance are unwarranted."

A one to two year follow-up study of 30 patients by Hartleb[56] showed recurrences in all but 10; some of these had followed a diet for ulcer subsequent to treatment with histidine. As in other series, many of the immediate results were good.

In a special article in the *Medical Journal of Australia* Maddox[57] gives an excellent and concise summary of the experimental and clinical work on the histidine treatment of peptic ulcer. That histidine can relieve pain is evident, and its economic advantage alone is of vast importance. However, this method has not yet had sufficient clinical trial to

55. Martin, K. A.: Histidine Hydrochloride Versus Diet and Alkalis in Treatment of Peptic Ulcer, J. A. M. A. **106**:1468 (April 25) 1936.

56. Hartleb, H. O.: Unsere Erfahrungen mit Larostidin bei ulcus ventriculi bzw. duodeni, Med. Klin. **32**:458, 1936.

57. Maddox, K.: Histidine Treatment of Peptic Ulcers, M. J. Australia **1**: 724, 1936.

warrant the discarding of other forms of treatment. At present it is of no known prophylactic value.

A series of 32 patients with peptic ulcer who received histidine treatment is reported on from Paris by Feldheim.[58] The lesions were in the stomach in 6 instances and in the duodenum in 26. The patients were divided into two groups, the first, comprised of 18 patients, receiving only histidine therapy and the second, comprised of 14 patients, receiving additional medical treatment. In the first group pain ceased in almost every case on the third or fourth day of the injections, and nearly all the patients gained weight. In only 3 patients did the direct signs of hypermotility and hypersecretion seem altered. In the second group were 10 patients whose pain had not previously been relieved by the usual forms of dietary, alkali and atropine treatment. Five of these patients remained unrelieved. In only 1 instance in this group did roentgenograms show any improvement in the ulcer. The conclusion is that histidine does not influence the ulcer but that the symptom pain is relieved. Histidine treatment alone is not sufficient, but it has a definite therapeutic rôle in conjunction with other forms of medical treatment.

The numerous clinical reports of the beneficial effects of histidine therapy on peptic ulcer have aroused much curiosity. Schürch and Blangey [59] devised some experiments on young dogs to facilitate direct observations on the course of the lesions. They were able to produce typical chronic gastric and duodenal ulcers in dogs with radium. In 22 of the 27 dogs chronic ulcers developed; treatment consisted of injections of a 4 per cent solution of levohistidine monohydrochloride in an isotonic medium. Thirteen of 17 other dogs with similarly produced ulcerations served as a control series, receiving no injections. The dogs that were given histidine showed much less tendency to perforation and bleeding than the untreated animals. Also, the dogs which were treated showed a definite macroscopic and microscopic tendency toward healing of the ulcerating process as compared to the lack of healing in the control series. The authors state that no far-reaching conclusions can be drawn from this as yet unconfirmed work, particularly in relation to clinical practice.

The histidine treatment of peptic ulcer has been critically reviewed by Barry and Florey,[60] with special attention to the animal experiments on which clinical trial has been based. They have contributed some interesting operative experiments on cats and pigs to determine the effect

58. Feldheim, E.: L'histidine dans la thérapeutique des ulcères gastro-duodénaux, Presse méd. **44**:1189, 1936.

59. Schürch, O., and Blangey, R.: Experimentelle Untersuchungen über die Wirkung des Larostidins beim Magengeschwür, Deutsche Ztschr. f. Chir. **247**: 590, 1936.

60. Barry, H. C., and Florey, H. W.: Histidine Treatment of Peptic Ulcer, Lancet **2**:728, 1936.

of histidine on ulcers produced in these animals. The results of operation on experimental Meckel's diverticulum in cats showed chronic ulcers in the ileal loop in all 9 animals of the control series and also in a number of the 9 animals treated with histidine. Of 4 growing pigs operated on, the 1 control and all 3 which received histidine showed characteristic chronic peptic ulcers. It is emphasized that Aron's observations on dogs similarly operated on were too few, the animals were not observed over a sufficiently long period and other investigators have not obtained the same seemingly favorable results. Although most clinical reports favor the use of histidine, at least as an agent for symptomatic relief, there is still little proof that histidine has any specific action on peptic ulcer.

Gastric ulcers have been produced experimentally in rats by feeding pepsin-hydrochloric acid. Windwer and Matzner [61] tested the therapeutic effect of injections of histidine monohydrochloride on rats with ulcers. In over 90 per cent of both the control group of rats and the group receiving the injections gastric lesions developed. In half of the 10 rats receiving histidine but no acid and no pepsin, gastric lesions developed, while a control group without histidine remained normal. The authors' inability to prevent gastric ulcers in rats with injections of histidine is contrary to a previous favorable report but is in keeping with similar work on other animals. It is suggested that the development of gastric lesions in rats on a normal diet plus histidine is due to the conversion of histidine into histamine, thereby adversely influencing a gastric defect. The question is raised whether or not this could occur in man.

EXPERIMENTAL GASTRIC EROSION (ULCER) PRODUCED BY A DEFICIENT DIET

Seven years ago Dam [62] reported erosions of the gizzard in chickens with hemorrhagic disease due to dietary deficiency, later termed fowl hemophilia. Only in the last year has attention shifted from this blood dyscrasia to the gastric lesions. As these lesions have been studied up to now only by those interested primarily in the poultry industry and not by clinicians, they have continued to be designated as gizzard erosions. I have examined about two hundred and fifty gizzards containing these lesions. It is evident that they are similar to the superficial gastric ulcers (erosions) in man and that in a number of instances chronic ulcers have developed which have involved the submucosa. Gastritis is also present. As these gastric ulcers are due to a dietary deficiency and may be prevented by an adequate diet, their occurrence in the chick is of major experimental interest.

61. Windwer, C., and Matzner, M. J.: Histidine in Experimental Gastric Ulcer, Am. J. Digest. Dis. & Nutrition **3**:547, 1936.

62. Dam, H.: Cholesterinstoffwechsel in Hühnereiern und Hühnchen, Biochem. Ztschr. **215**:475, 1929.

Dam and Schonheyder [63] again note the presence of these ulcers in chicken gizzards and the details of the feeding experiments by which they may be produced, but Almquist and Stokstad [64] add considerable information regarding the development and prevention of the ulcerating lesions. The erosions are produced by placing newly hatched chicks on a diet lacking in all greens and all grain except rice flour and containing adequate amounts of the previously known vitamins. A hemorrhagic diathesis due to the lack of vitamin K develops in the third and fourth weeks, and if the birds die or are killed at the end of four weeks, almost 100 per cent show erosions of the gizzard to a moderate or marked degree. It was originally thought that the erosions were due purely to vitamin K deficiency. Adding alfalfa, kale, hempseed or wheat bran in adequate amounts (5 to 25 per cent of the diet) prevented the development of the lesions. Many other substances were tested for the presence of this antierosion factor, but they were all deficient.

A further series of feeding experiments revealed that extracts of certain greens were also preventive but that a far larger amount was required to prevent the formation of gastric erosions than to prevent hemorrhage. It was shown that vitamin K was in the nonsaponifiable fraction of alfalfa and that this fraction did not contain the antierosion factor. However, the saponifiable fraction did contain this factor, definitely proving that it is not identical with vitamin K; it is also readily destroyed by heat, but vitamin K is not.

It is evident that erosions (ulcers) of the gizzard in chicks caused by a deficiency in diet are due to a lack of a fat-soluble factor which is comparatively unstable and which is not identical with any of the known vitamins. When certain greens and cereals or their extracts which contain this factor are added to the diet, they prevent the development of the gastric lesions. In conjunction with this ability of an unknown dietary substance to protect the gastric mucosa from erosion, it should be stated that I have found that it is also curative. If the lesions are allowed to develop on a deficient diet and adequate amounts of alfalfa are added, restoration to a normal-appearing mucosa will take place within about three weeks.

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63. Dam, H., and Schonheyder, F.: Occurrence and Chemical Nature of Vitamin K, Biochem. J. **30**:897, 1936.

64. Almquist, H. J., and Stokstad, E. L. R.: A Nutritional Deficiency Causing Gizzard Erosions in Chicks, Nature, London **137**:581, 1936; The Gizzard Factor of the Chick, J. Nutrition **13**:339, 1937.

Obituary

JOSEPH L. MILLER, M.D.
1867-1937

It is with a sense of deep regret and of great personal loss that the ARCHIVES OF INTERNAL MEDICINE records the death of Joseph Leggett Miller, its Editor in Chief for many years. To his devoted labors and high scientific ideals the ARCHIVES acknowledges a great debt of gratitude for whatever service it has been to medical literature.

Dr. Miller was born in Kewanee, Ill., in 1867. He graduated with a bachelor's degree from the University of Michigan and received his medical degree from Northwestern University. After graduation he entered Mercy Hospital, in Chicago, as an intern, where he served for a time with Dr. Christian Fenger. Soon after his internship he became associated with Dr. Frank Billings, and this relation continued during all the years of Dr. Billings' practice.

Dr. Miller's interest in teaching led to his appointment as instructor at Northwestern University and later at Rush Medical College, where he was promoted to an associate professorship. For the last ten years of his life he was clinical professor of medicine at the University of Chicago.

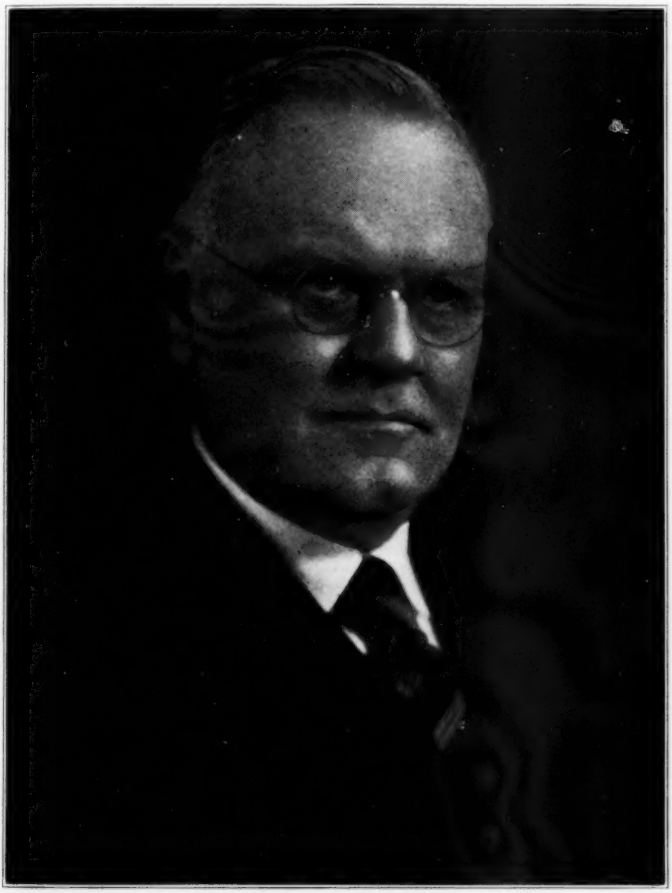
For twenty years he served on the attending staff of the Cook County Hospital, and for a long time, as president of the staff. He was senior physician at St. Luke's Hospital for the last eighteen years and sometime president of the medical board. To St. Luke's Hospital, as to all other interests, he gave unselfishly of his time and effort.

Always active in medical societies, Dr. Miller was a charter member and later president of the American Society for Clinical Investigation, and a member of the Association of American Physicians and of the Central Society for Clinical Research. He presided one year as Chairman of the Section on Medicine of the American Medical Association. He was also president of the Chicago Institute of Medicine. The results of his own clinical experience and investigation and his helpful discussion of the work of others added much to the proceedings of these societies. One of his outstanding traits was his interest in younger men and his eagerness to help and encourage them in their clinical and investigative work by his advice and counsel.

In 1918 Dr. Miller entered the United States Army as major and was later promoted to the rank of lieutenant-colonel.

Early in his career Dr. Miller was determined to spend part of his time in research. His contributions covered a wide field, including the etiology of arteriosclerosis, typhoid, foreign protein therapy, nephritis, arthritis and thyrotoxicosis.

Aside from his scientific interests, Dr. Miller was an enthusiastic sportsman. No fisherman was ever more eager for the arrival of the trout season. For a week or two before going to Montana one year he was so preoccupied with rods and lines and flies that a patient



JOSEPH L. MILLER, M.D.
1867-1937

coming out of his office remarked, "It's no use consulting Dr. Miller when the trout are biting. He talked of nothing but his trip and advised me for my arthritis to go fishing."

Dr. Miller's courage and honesty won him a host of friends. His example as a citizen, a patriot, a wise teacher and a scholar will long be cherished.

Book Reviews

Lane Medical Lectures: Studies in Cardiovascular Regulation. By G. V. Anrep, M.D., D.Sc., F.R.S., Professor of Physiology, the Medical Faculty of the Egyptian University, Cairo. Stanford University Publications, University Series, Medical Sciences, Vol. 3, No. 3. Paper. Price, $1.50. Pp. 118. Stanford University, Calif.: Stanford University Press, 1936.

This volume contains the series of five lectures by Anrep given in 1936 under the sponsorship of the Lane Medical Lecture Fund at Leland Stanford University. This series is devoted to circulatory physiology and is divided into the following subjects: (1) the proprioceptive mechanism of cardiovascular regulation, (2) respiratory regulation of the heart rate, (3) the dynamics of the coronary circulation, (4) the coronary blood flow and (5) the blood flow through skeletal and plain muscles.

These lectures represent a comprehensive discussion of the important experimental work in this field of physiologic research, a field in which the author's personal contributions have been outstanding.

The first two lectures are primarily a report of numerous experiments with regard to the control of the heart rate, showing the effects of changes in the pressure in the aorta and in the carotid sinus, in the oxygen and the carbon dioxide content of the blood and in the reflexes involved in the extremely complex mechanism by which the heart adapts itself, a mechanism which the author has chosen to call the proprioceptive mechanism of cardiovascular regulation.

The lectures that were most interesting to the reviewer were the two on the coronary circulation. The author cites experimental data in support of the opinion that "The contraction of the ventricle, certainly far from favoring the blood [coronary] flow, definitely impedes it. The forward rush of blood into the coronary artery which occurs during the systolic rise of the aortic blood pressure is determined by the elasticity of the coronary vessel and is not a measure of the coronary blood flow. The main blood flow through the coronary system takes place in diastole." Changes in blood pressure, the effects of cardiac rate and of changes in the oxygen and the carbon dioxide content of blood in their effect on coronary blood flow in the denervated heart are discussed. Also, the extremely difficult work on the innervated heart in the study of the influence of the vasomotor reflexes on the coronary blood flow is extremely valuable and of more than academic interest. To those whose interest is primarily in cardiovascular physiology this group of lectures should be very welcome.

On the Incidence of Anaesthetic Complications and Their Relation to Basal Narcosis. By C. J. M. Dawkins. Price, 3s. 6 d. Pp. 56. London: Middlesex Hospital Press, 1936.

An analysis of approximately sixteen thousand anesthetics given at several London hospitals and by the author is presented. Complications occurring during and after anesthesia are briefly considered. In two large comparable series two deaths directly attributable to the anesthetic occurred when the basal narcotic was used. The morbidity of pulmonary complications was doubled by the use of the basal narcotics, bronchitis and atelectasis being the most common. Operations involving the abdomen most frequently showed anesthetic complications. Postoperative care to prevent complications is considered.

The safest general anesthetic given was "nitrous-oxide-oxygen," supplemented by ether as needed. Other anesthetics were rarely used, because of contraindications and complications from the anesthetics themselves. Divinyl ether and cyclo-

propane have not been used enough to warrant deductions. The basal narcotics used included tribromethanol in amylene hydrate, paraldehyde and assorted barbiturates, the latter both orally and intravenously. The author prefers paraldehyde rectally as a basal narcotic, though small doses intravenously of evipal (N-methylcyclohexenylmethylmalonylurea) are used frequently.

The presentation would have been more valuable if more definite indications and contraindications regarding the use of basal narcotics had been given. In parts it is rather difficult to follow the "route" of the author's analysis. Complete statistical details and a good bibliography of both European and American literature are given. The author's conclusion that basal narcotics should not be used as a routine measure but only in certain cases, and this only with full realization of the possible complications as compared to the probable benefits, seems well justified from this analysis.

An Index of Differential Diagnosis of Main Symptoms. By Various Writers. Edited by Herbert French. Fifth Edition. Price, $16. Pp. 1,145 (218 pages of index), with 742 illustrations. Baltimore: William Wood & Company, 1936.

Since this book is in its fifth edition, it is safe to say that it has filled a necessary place in the reference libraries of many physicians. If the diagnosis of disease is made easier by a thorough indexing of the symptoms, this book attains its purpose. For example, the symptom diarrhea is mentioned more than one hundred and fifty times in the index, but about ninety of these references are found on five pages. However, the rest of the references (approximately sixty) are scattered from pages 2 to 919. This is not the end of the cross-indexing of this symptom, for under "Abdomen, distention of" it is referred to as "hill diarrhea," and, finally, the symptom is last mentioned under "Zymotic diarrhea." As diarrhea is indexed, so are the other common symptoms of disease indexed. Furthermore, there is no differentiation between the terms "symptom" and "sign." They are both referred to as symptoms.

The medical student who has not finished the fifth year of medicine does not have sufficient critical judgment to use the book. The specialist will find that it falls short of his needs. The general practitioner with a limited library will no doubt find it of value.

It can be said that this book contains the most extensive cross-indexing of the signs and symptoms of disease in the English language. The difficult task of compiling such an index has been thoroughly accomplished. When and where there is need for such an index, this book may be highly recommended.

Diseases of the Coronary Arteries and Cardiac Pain. Edited by Robert L. Levy, M.D., Professor of Clinical Medicine, Columbia University. Price, $6. Pp. 451, with 94 illustrations. New York: The Macmillan Company, 1936.

This monograph, on a subject of great interest to all practitioners, was prepared by a group of fourteen well known specialists, each of whom wrote one or more chapters on some phase of cardiac pain in which he is particularly interested. The result is a comprehensive volume. The manner in which the editor has assembled the material is attractive, the printing is good and the illustrations and tables that appear are clear and easily understandable.

As regards contents, all one can say is that each chapter is delightfully written and is accompanied with a good bibliography. The various phases of cardiac pain are discussed, all the way from the early history of angina pectoris and coronary occlusion through the physiology, pathology and clinical manifestations of these disorders to their most recent therapeutic attack by modern surgical methods. On the whole, the book is extremely good; it can be enthusiastically recommended to students and practitioners alike.

Medizinische Praxis. Edited by R. L. Grote, A. Fromme and K. Warnekros. Volume XIV. **Elektrokardiographie für die ärtzliche Praxis.** By Erich Boden, M.D., Professor of Medicine in Düsseldorf. Third Edition. Paper. Price, 10 marks. Pp. 203, with 104 illustrations. Dresden: Theodor Steinkopff, 1936.

Without doubt this is a useful booklet and deserves continued recognition by American clinicians. The first edition appeared in 1932 and was reviewed in the ARCHIVES OF INTERNAL MEDICINE (**51**:640-641 [April] 1933). It was stated that this little volume was an admirable elementary exposition of electrocardiography for the practitioner, and particular praise was given the tracings and diagrams. The third edition is much like the first, with reasonable amplification. Again the illustrations are outstanding and commendable. Again the latest edition continues to be no more than was originally intended, a first rate elementary exposition of electrocardiography for any practitioner interested in cardiac disease.

Recent Advances in Endocrinology. By A. T. Cameron. Third Edition. Price, $5. Pp. 458, with 65 illustrations. Philadelphia: P. Blakiston's Son & Co., 1936.

This splendid little book contains more than merely the recent advances in endocrinology. It is really a small textbook. The subject is treated in a scholarly way and is supplemented with an extensive bibliography, photographs and charts. One is surprised to find how much important material has been compressed into a brief space. The book should be equally useful to the physiologist and to the clinician.